VOLUME 60 • NOVEMBER 1958 • NUMBER 5

# OPHTHALMOLOGY

Slit-Lamp Examination of the Fundus
*Dohrmann K. Pischel*

The Hyaluronic Acid in the Rabbit Vitreous Body
*Godfred Larsen*

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The Fine Structure of the Lens Epithelium
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*Gösta Karpe*

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# A. M. A.
# ARCHIVES OF OPHTHALMOLOGY

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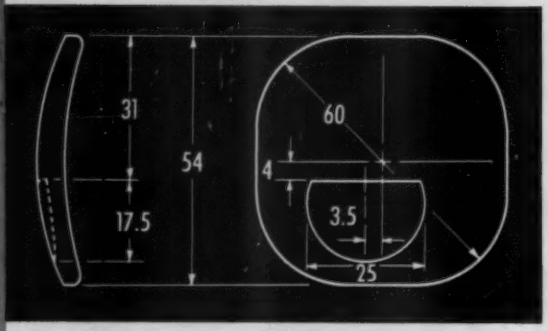


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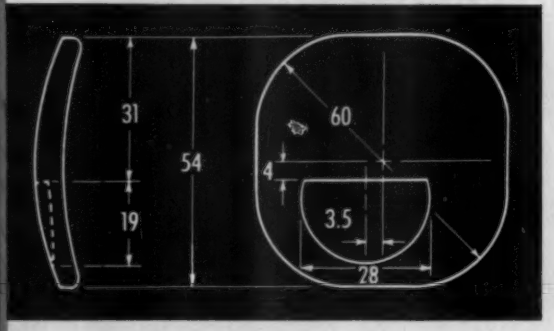


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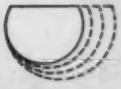

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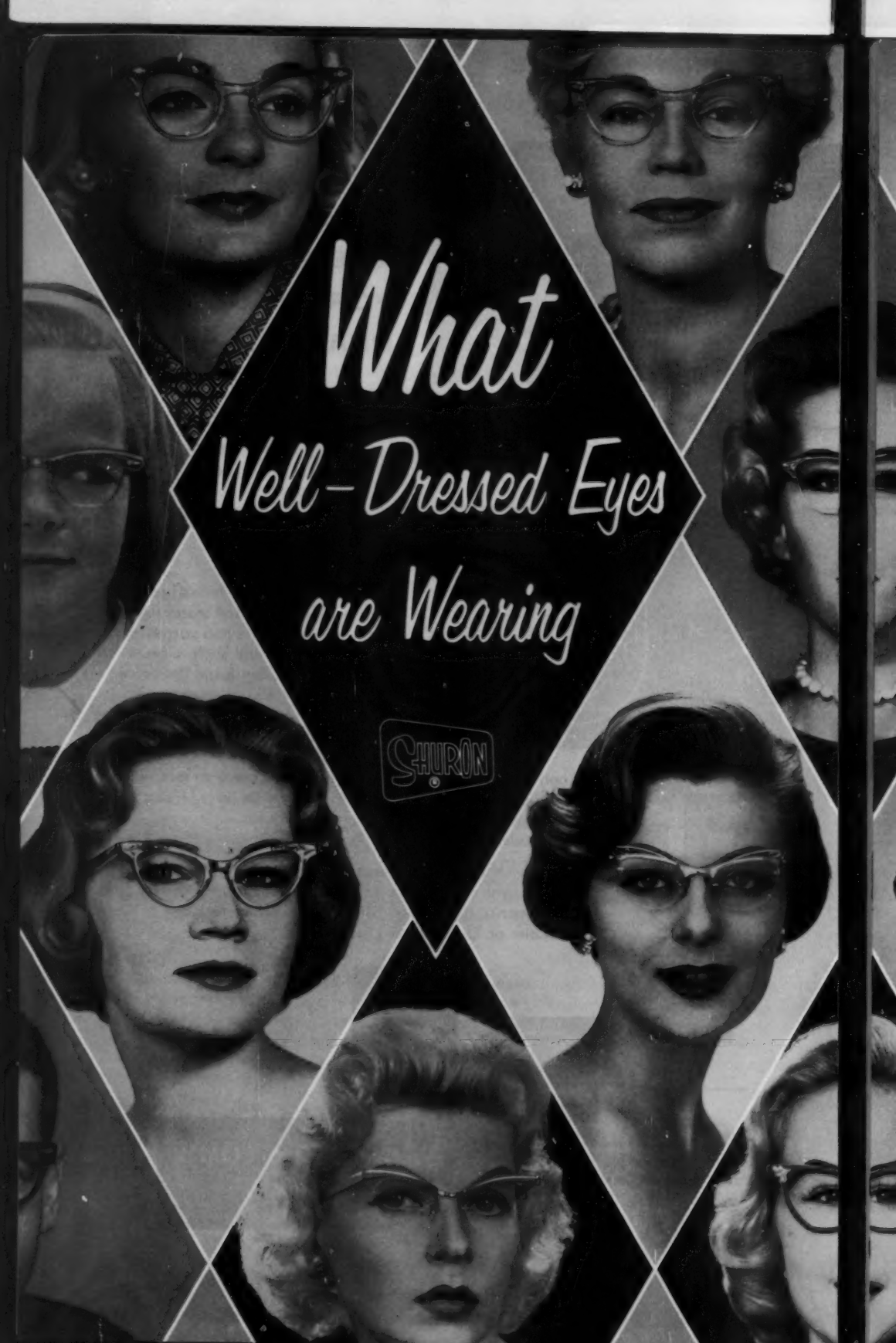
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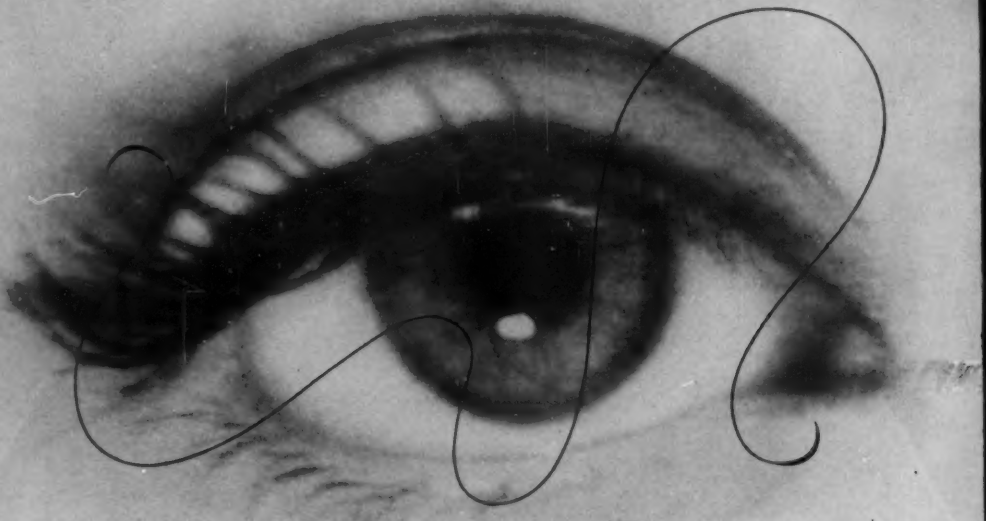

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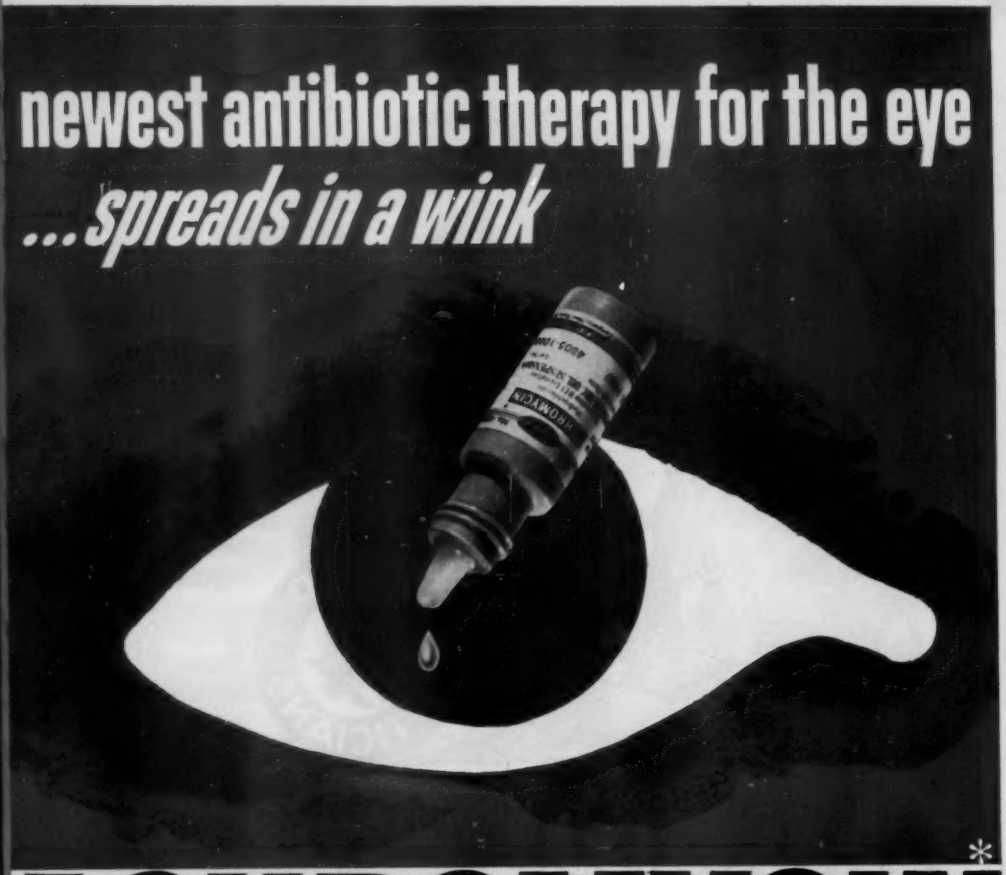

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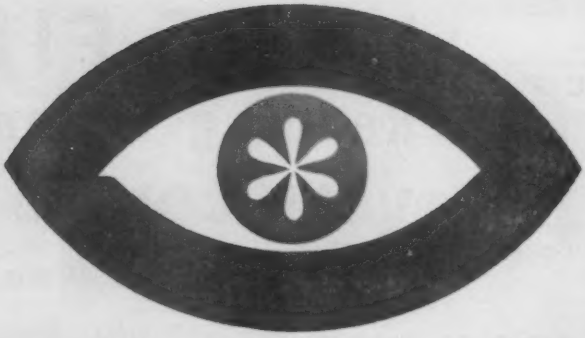

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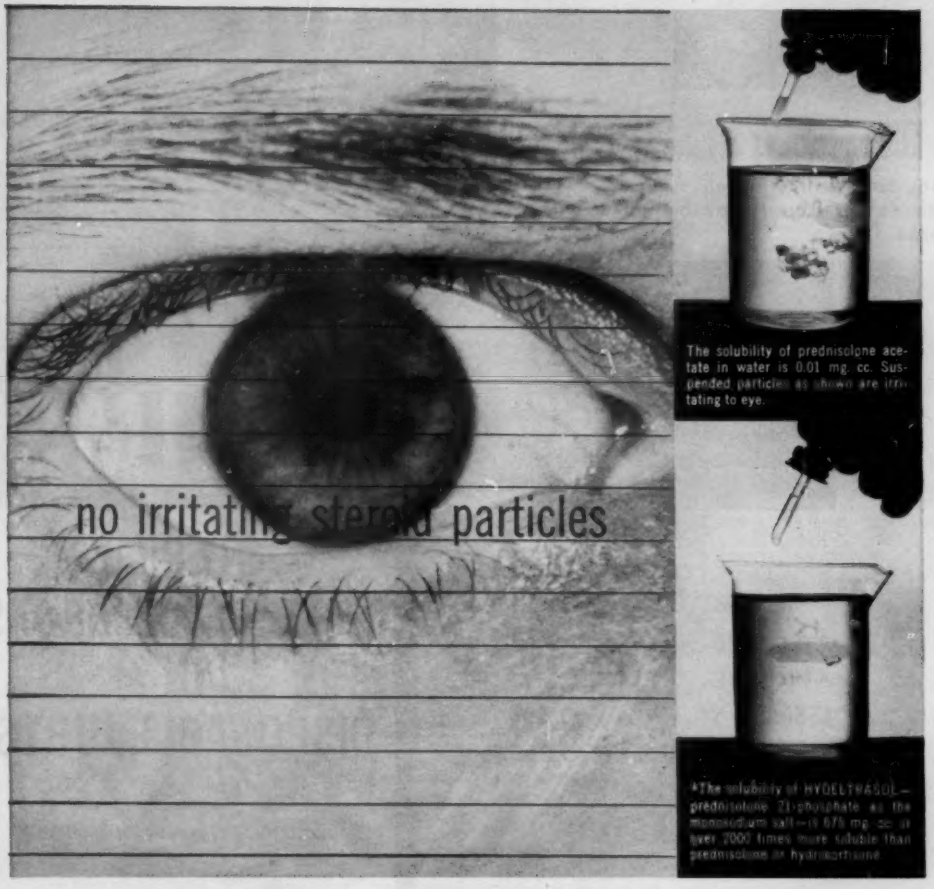
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2. Emmerich, R.; Carter, G. Z., and Berens, C.: Am. J. Ophth. *40*:841 (Dec.) 1955.

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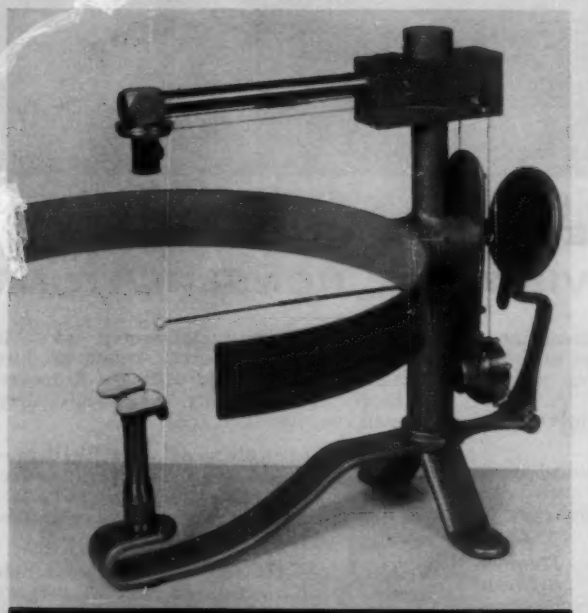

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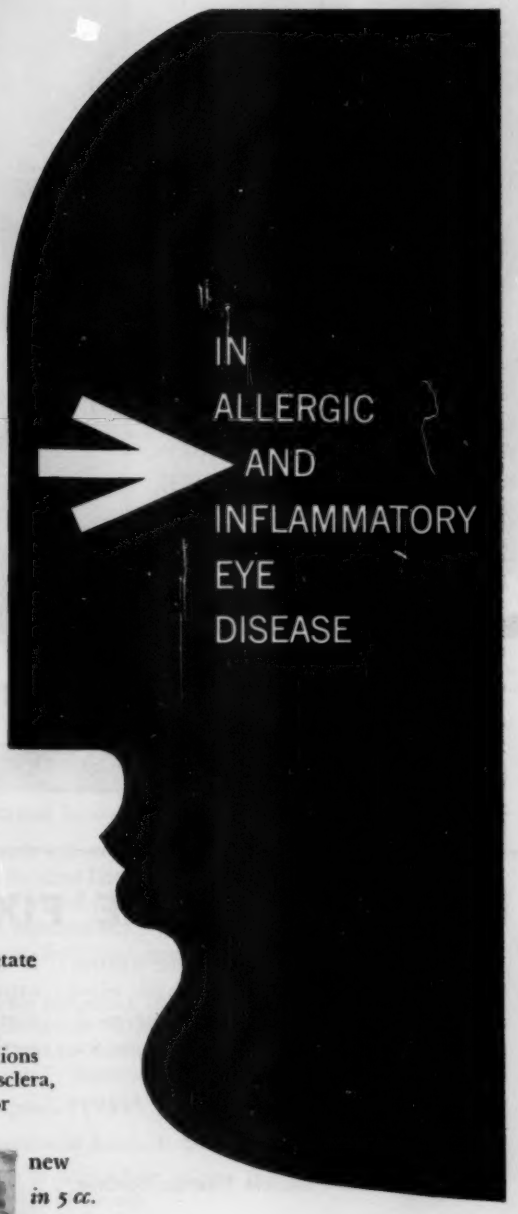


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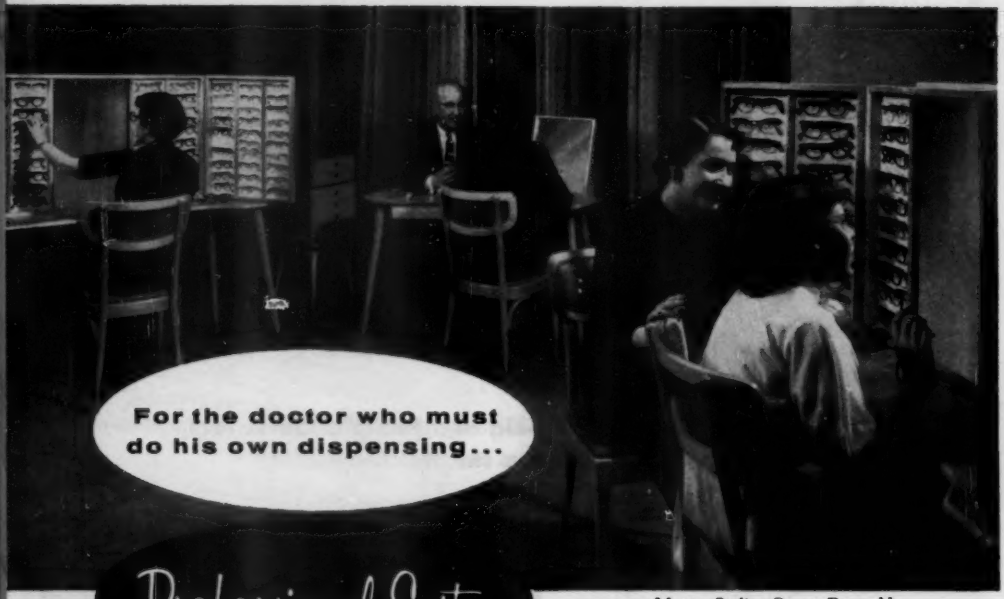


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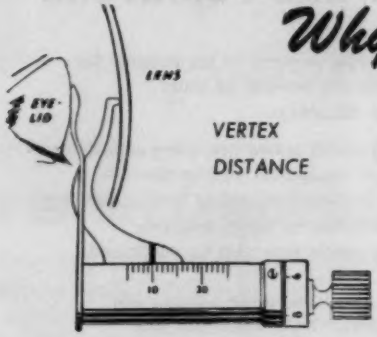


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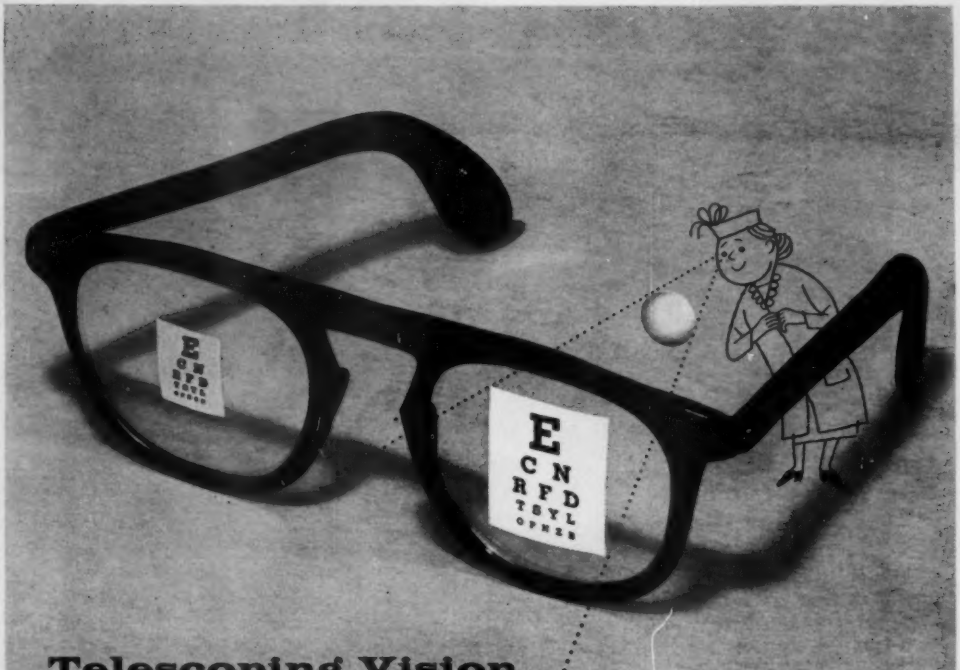

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# Slit-Lamp Examination of the Fundus

DOHRMANN K. PISCHEL, M.D., San Francisco

Owing to the great interest in retinal detachment surgery at the present time, there are frequent reports of the best manner in which one should examine the fundus ophthalmoscopically. Proponents of indirect ophthalmoscopy vigorously support this as a new method, which as a matter of fact was first proposed and practiced by Sichel in 1885 and Galezavski in 1886.

It is perhaps discouraging to realize that it has taken almost 75 years for one method of fundus examination to achieve considerable acceptance. Therefore, I believe that one should not feel too discouraged when another method of fundus examination makes slow progress in being generally practiced. I am referring to the much neglected slit-lamp examination of the whole fundus. This most valuable technique is little understood and still less practiced. As the slit lamp really dates from the work of the great Swedish ophthalmologist Alvar Gullstrand, in about 1911, and therefore the method is only about 50 years old, I suppose one should feel encouraged that we have only 25 years of missionary work ahead of us before the slit-lamp examination of the whole fundus becomes routine. Seriously, I have hopes for much faster progress. The instrument makers are eagerly producing new major instruments and many types of auxiliary equipment to facilitate this type of examination. Some of this is very good; some is very poor, and much needs only a little alteration to make it very good. In a paper written five years ago, I described in detail the technique necessary for the examination of the vitreous. As this technique is the same as for the fundus in general, only a brief review will be given here.

To make the examination of the deep fundus of the eye practical with the slit lamp, two changes must be made in the usual technique. First, the angle between the slit-lamp beam entering the eye and the line of sight of the binocular microscope must be reduced to at least 17 degrees. Second, the refractive power of the eye must be practically abolished. The first change, i. e., reduction of the angle between the line of the light beam and the line of sight, has gone through several modifications, and today the problem has several solutions. With the older type of slit lamps, such as the Zeiss and similar models, it was necessary to put a mirror on the end of the slit-lamp arm, so that the light could be reflected into the eye, even with the arm pushed to one side away from the observer's head. This system can still be used by those who have this type of equipment, but it requires considerable skill and practice and at best it is sometimes very frustrating. This system requires considerable adjustment of the position of the slit-lamp arm, the angle of the mirror, and the focus of the slit-lamp beam. In addition to this, the

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microscope must be focused on the plane on which the beam is focused. This is very difficult to do. Lindner sought to simplify matters by his off-set monocular microscope. This eliminated many of the adjustments of the slit-lamp lighting system but lost the value of binocular vision.

The great step forward was provided by Goldman. He kept the principle of the slit lamp with its arm and condensing lens, added his double reflecting prism to obviate the previously needed mirror, and then coupled the slit-lamp arm to the microscope in such a way that they both could be kept focused at the same plane in the eye at all times. To focus deeper or more shallowly was accomplished by moving a simple lever, or "joy stick." This was the crux of the whole situation. This splendidly designed slit lamp made the examination of the deeper fundus easy for everyone. Nevertheless, it took a surprisingly long time before an appreciable number of ophthalmologists realized the advantages of this new system.

Since then, this system of coupling together the slit-lamp light system and the microscope has been adopted by all makers of slit lamps. All slit lamps now made provide for the reduction of the angle between the slit-lamp beam and the line of sight of the corneal microscope to less than 17 degrees. Reduction of the angle to zero is a mistake. If this is done, the lines of sight and of light are practically the same and one is using the system of illumination of the binocular ophthalmoscope, as in the large Bausch and Lomb binocular ophthalmoscope. In doing this one loses the advantage of the slit-lamp miomicroscopy, which consists in the ability to examine a very thin optical section of some tissue. To be able to see this section, one must look at it from an angle, so as to see its proximal surface. If one views it directly from in front, one sees only the anterior surface of the illuminated tissue.

The second change from the usual slit-lamp technique, the reduction of the refractive power of the eye, was accomplished by Koeppe with his flat-surfaced contact glass. This glass was placed on the cornea and held in place by the lids. This change was modified by various men. It necessitates the anesthetizing of the cornea and conjunctiva and requires some skill in its placement on the eye. In very nervous patients and children it could not be used. Such a glass allowed examination of the retina for about 20 degrees to all sides of the macula, but the equator could not be visualized.

Other types of contact lenses have been introduced. Thorpe introduced his gonioprism, and Allen, the Lee-Allen contact glass. Both of these rested on the cornea and were chiefly used for viewing the anterior chamber angle.

More recently, Goldman has developed his contact glass with three reflecting mirrors set at different angles. This again is a great step forward. With it one can examine the posterior pole as with any contact glass. Then, by means of the appropriate mirror, one can examine the region of the equator, the region anterior to the equator, and, with the most acutely angled mirror, the ora serrata and the angle of the chamber, thus combining ophthalmoscopy with gonioscopy.

A means of further simplifying the fundus examination was suggested by Hruby, who advocated a preset lens of −55 D. to replace the contact lens. This had the feature that no contact with the cornea was necessary, which was a big advantage by itself. But further very important advantages were provided. By displacing the preset glass to one side or the other, or far above or below the center of the cornea, it became possible to see the retina far anterior to the equator.

Summing up, then, for the technique of fundus examination with the slit lamp one needs first a slit lamp whose beam can be brought to within 17 degrees of the line of sight of the corneal microscope either by a Goldman prism or by placing the lamp housing in the proper position. Then one

needs a means of abolishing the refractive power of the eye with a contact lens or a preset lens (Hruby lens).

Which lens is the best? Each has its place. The ease with which the preset lens can be placed in front of the eye makes it simple to use in every slit-lamp examination, with no expenditure of time. By use of the peripheral portions of this lens its strong prism action enables one to examine the fundus up to and well anterior to the equator. It does, however, minify the image seen. The contact glass, on the other hand, gives a larger image, and the Goldman type allows one to see very far anteriorly. One probably would feel that, as it needs to be placed over an anesthetized cornea, one would tend to use it in selected cases, instead of on each and every patient.

In everyday practice what are the uses for slit-lamp examination of the fundus? The examination of the macula and optic disc are, of course, obvious. Very early and slight papilledema can be diagnosed with the slit lamp. The many changes at the macula in older patients can also be seen in a new light. Edema of the macula is easily recognized and minute cysts can be seen, which will explain a patient's loss of vision. Larger cysts of the macula can be differentiated from holes in the macula. This is of tremendous value in deciding whether such a "hole" needs treatment by coagulation or whether it can safely be left alone. The approximate layer in which some type of exudate or yellow mass is located can also be determined. Whether hemorrhages are in the nerve fiber layer or deep in the retina can be determined. The presence of fine proliferating tissue on the surface of the retina can be determined. In cases of retinal detachment, the presence of such tissue, especially when bridging over retinal folds or star figures, will give tremendous help in determining the type and extent of operation needed. Small holes in a detached retina can be seen and accurately differentiated from cysts or thin areas. Very flat detachments of the retina are readily discovered.

The vitreous can be examined through all its portions, as was described in the previously mentioned paper. Many important findings will be brought to light. It can be determined if hemorrhages are in the vitreous substance itself or if they are in the subvitreal space, that is, in the space between a shrunken and detached vitreous and the retina. These latter will probably absorb very quickly, in contradistinction to those in the vitreous itself. A patient may present himself with the complaint of a spot or circle before one eye, perhaps preceded by seeing flashes of light. The presence of a detached vitreous, often with an opacity on its posterior face, can usually be readily seen in such a case. If this opacity is the "ring opacity" or one of similar form due to the detachment of the vitreous from its attachment at the disc, such a patient can be reassured as to the harmlessness of the situation.

However, if slit-lamp examination reveals a more solid opacity on the posterior face, it may indicate that an operculum has been torn out of the retina. The corresponding retinal hole can then often be found, owing to the clue given by the position of the operculum. Such a patient can then be warned of the situation.

In cases of retinal detachment, the vitreous can usually be traced to the flap of a horseshoe tear, and the influence of this condition on the whole situation must be taken into account. Furthermore, in a retinal detachment cured by operation the flap of a tear may still be seen protruding into the fundus, and if the vitreous is still adherent to it the examiner knows that the case must be followed most carefully, whereas if the vitreous has pulled free from the flap the case can be considered very safely healed.

I have purposely left to the last the most important help the slit-lamp examination of the fundus can give. This is in the differential diagnosis of a simple retinal detachment from a retinal detachment caused by a small choroidal tumor or malignant melanoma.

There is no difficulty in this differential diagnosis if the tumor is large, filling one quarter or more of the fundus. The difficulty is with the small tumor, perhaps only three or four D. D. large. Aids to a differential diagnosis by means other than the slit lamp have been published by me before, and so only a brief review will be made here. Ophthalmoscopically an elevated retina with a tumor beneath it will have a mottled appearance. It will rise rather rapidly from the surrounding level of retina, and in the periphery it will drop off rapidly to the level of the attached retina. No motion will be detected, and even with the ophthalmoscope the suspicious area will not look translucent.

As mentioned elsewhere, transscleral transillumination has proved absolutely unsatisfactory to me. If the tumor is large enough to cast a definite shadow, it is so large that no difficulty arises in the differential diagnosis. If the tumor is small, even as large as 1 to 1.5 cm. in diameter, transscleral transillumination will almost always reveal no shadow.

When the suspicious area is viewed from the front with intense light the situation is quite different. Some ophthalmologists call this type of examination anterior transillumination. I, however, feel that a better term is focal illumination of the fundus, which is similar to focal illumination of the anterior segment of the eye. When performed by means of the slit lamp, it is very accurate and practically pathognomonic. The observer must be familiar with slit-lamp fundus examination and know the characteristic appearance of simple retinal detachments. They are translucent, and often the beam of the slit lamp can be followed beneath the surface of the retina, with an appearance similar to a very heavy flare in the anterior chamber. The whole area of the detachment is usually equally translucent. Furthermore, on movements of the eye the retina can be seen to move. In some cases it floats freely, almost like the filmy fin of a tiny tropical fish; in other cases it may shake more like some jellied mass.

In the case of a tumor, there is an entirely different picture. While at the edge of the suspicious area the retina may be translucent, as soon as the beam strikes the area of the tumor there is no translucency whatsoever. The slit-lamp beam strikes the retina and penetrates no further. Usually a dark brown mass can be seen distinctly. At the edge of such a detachment the difference between the part that is a serious detachment and the part that is solid is most striking. Thus, the solid character of the detachment can be most definitely and accurately established. In recent years my experience at Stanford Medical School and in my practice has produced no false diagnosis in tumor cases.

I would feel, therefore, that the aid given by the slit lamp in such cases alone would definitely establish its usefulness in fundus examination. When one adds to this the other important types of lesions in which its use is of great value, the statement is justified that ability to make a good slit-lamp examination of the fundus is an absolute necessity in the practice of clinical ophthalmology.

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# The Hyaluronic Acid in the Rabbit Vitreous Body

*Variations Following Hormonal Treatment*

GODFRED LARSEN, M.D., New York

In a previous paper [1] the changes in the viscosity of the filtrate from rabbit vitreous induced by hormones have been published. Here the changes of the content of hyaluronic acid will be reported and the viscosity and concentration of hyaluronic acid, correlated to find out whether other factors than concentration might be responsible for the viscosity changes.

The hyaluronic acid was not determined directly, because no methods are available for estimating such small amounts of hyaluronic acid as are contained in single vitreous bodies. Therefore, the hexosamine method elaborated by Elson and Morgan (1933),[2] in Blix's modification, was used. Several authors (Meyer et al., 1936,[3] 1937,[4] 1938 [5]; Pirie, 1948 [6]; Balazs, 1954 [7]; Schweer et al., 1955,[8] 1956,[9,10] and others) have determined the hyaluronic acid as hexosamines, one of its components, and found this method, although not perfect, of sufficient accuracy for the purpose.

The hyaluronic acid is present in the interfibrillary fluid and seems not to be a part of the fibrillary network (Matoltsy, 1952 [11]; Nechel, 1953 [12] Schweer and Karell, 1956 [10]). Neutral mucopolysaccharides, on the other hand, (Dische, 1955 [13]) have been shown to be bound to the residual protein. Hexoses derived from these mucopolysaccharides do not, however, interfere with the determination of hexosamines. The distribution of hyaluronic acid throughout the vitreous humor is not uniform; Balazs (1954)[7] found a higher content in the posterior than in the anterior part; Schweer and Karell (1956)[10] were able to confirm the results of Balazs. Therefore, whole vitreous bodies were used through all the experiments.

## Material and Methods

Male rabbits weighing from 2000 to 3000 gm. were used for the experiments. Both the relative viscosity, i. e., viscosity of the vitreous filtrate compared with distilled water, and the hyaluronic acid were determined in the same samples; most of the viscosity figures are from a previous publication.[1] The animals were divided into five groups, of which 31 were used as controls; 25 were treated with cortisone, 25 to 50 mg. during 10 to 14 days; 25 were thyroidectomized; 30 were both thyroidectomized and given injections of thyrotropin,* 8 to 10 U. S. P. daily for 7 days, and, finally, 27 were submitted to treatment with thyroxin, 0.5 mg. daily through 7 days.

The hyaluronic acid was, as mentioned, measured as glucosamine following the method of Elson and Morgan in Blix's modification (1948).[14] The samples of vitreous bodies were prepared as described in a previous article. The left eyes of the rabbits were first removed, and the glucosamine was determined; two to three weeks later the right eyes were enucleated and the glucosamine content of these was compared with that of the left eyes; i. e., during all the experiments the left eyes were the control eyes and the right eyes, the treated

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Connective Tissue Research Laboratory, University Institute of Medical Anatomy, Copenhagen.

This investigation was aided by grants from Mr. and Mrs. Reinholdt, W. Jorck's Foundation, Merchant of Odense Johann and Hanne Weimann, nee Seedorff's Foundation, and the Danish Association Against Rheumatic Diseases.

* Supplied by Parke, Davis & Company, Detroit.

ones. As whole vitreous filtrates were used, being about 1.5 ml., every sample was weighed before the procedure was started. Also, determinations were done on nonfiltrated vitreous bodies, but they did not differ significantly from those of the filtrated samples. The preliminary depolymerization and hydrolysis was effectuated over a period of 48 hours in an incubator at 37 C by adding about 0.5 ml. of buffer solution of sodium chloride phosphate of pH 7, containing 200 V. R. U. per milliliter of hyaluronidase.† Althought a sterile technique was aimed at throughout, 1 drop of toluene was added to prevent possible decomposition of the hyaluronic acid. The proteins were removed by treating the samples with 2 ml. of 10% trichloroacetic acid followed by filtration through fine filter paper (Munktell, O. O.). Two milliliters of the mixture was then pipetted into a glass bulb with a stopcock, and 1 ml. of 6 N HCl was added to continue the hydrolysis in an air incubator for 14 hours at 100 C. Hereafter the content was carefully titrated with 5 N NaOH, using methyl red as an indicator. To the neutralized sample 4 ml. of acetyl acetone solution was added, and later the mixture was heated in a water bath at 96 C for about 30 minutes. After cooling, 2 ml. of the solution was dissolved in 96% alcohol. After addition of 2 ml. of Ehrlich reagent, the light absorption was measured in a Beckman spectrophotometer at the wavelength of 530 mμ, with use of 50 mm. cuvettes throughout. The glucosamine values were converted to those of hyaluronic acid by multiplying the observed glucosamine concentrations by the factor 2.43. This corresponds to a glucosamine content of 41.5% of the protein-free hyaluronate preparation used as the control. For determining the calibration curve, solutions containing 5 mg. glucosamine per 100 ml. were used. Various concentrations, ranging from 0.315 to 5.0 mg. per 100 ml., were made, and the observed glucosamine values were compared with the theoretical ones. All readings were done three or more times on the photometer; the average value observed was used as the final one.

† Penetrase Leo, supplied by the Leo Pharmaceutical Factories, Copenhagen.

TABLE 1.—*Differences of Observed Glucosamine Values from Theoretical Ones in Series of Glucosamine Determinations*

| Theoretical Conc., Mg.% | Observed Conc., Mg.% | Theoretical Conc., Mg.% | Observed Conc., Mg.% |
|---|---|---|---|
| 0.62 | 0.54 | 1.25 | 1.29 |
| ---- | 0.62 | ---- | 1.24 |
| ---- | 0.56 | ---- | 1.19 |
| ---- | 0.54 | ---- | 1.17 |
| ---- | 0.66 | ---- | 1.28 |
| ---- | 0.64 | ---- | 1.18 |
| ---- | 0.54 | ---- | 1.20 |
| ---- | 0.57 | ---- | 1.30 |
| ---- | 0.65 | ---- | 1.17 |
| ---- | 0.58 | ---- | 1.21 |
| $\sigma$ = 0.031 as percentage of average conc. ± 8.2 | | $\sigma$ = 0.051 as percentage of average conc. ± 4.2 | |

## Results

The content of hyaluronic acid was found to be very low, the amount of glucosamine present in the normal neutralized sample being only about 7.5μg. This made the use of 50 mm. cuvettes, as suggested by Blix, necessary. As these values were so close to the borderline of accuracy of the method, sev-

TABLE 2.—*The Concentration of Hyaluronic Acid in Vitreous Bodies from Normal Rabbits* *

| Group | Cases, No. | Relative Viscosity | | Hyaluronic Acid, Mg. % | | |
|---|---|---|---|---|---|---|
| | | Range | $M$ | Range | $M \pm (\varepsilon M)$ | $\sigma$ |
| Left eye | 31 | 1.113-1.196 | 1.114 | 2.48-3.60 | 2.85±0.056 | 0.306 |
| Right eye | 31 | 1.110-1.204 | 1.146 | 2.43-3.65 | 2.86±0.058 | 0.308 |

* Differences between left and right eyes with regard to average hyaluronic acid concentration. $D$=(mean difference)=0.0123; $t$ (according to "Student")=0.7476; $P$ (significant level)=0.5; $M$=arithmetic mean; $\varepsilon(M)$=standard error of mean; $\sigma$=standard deviation.

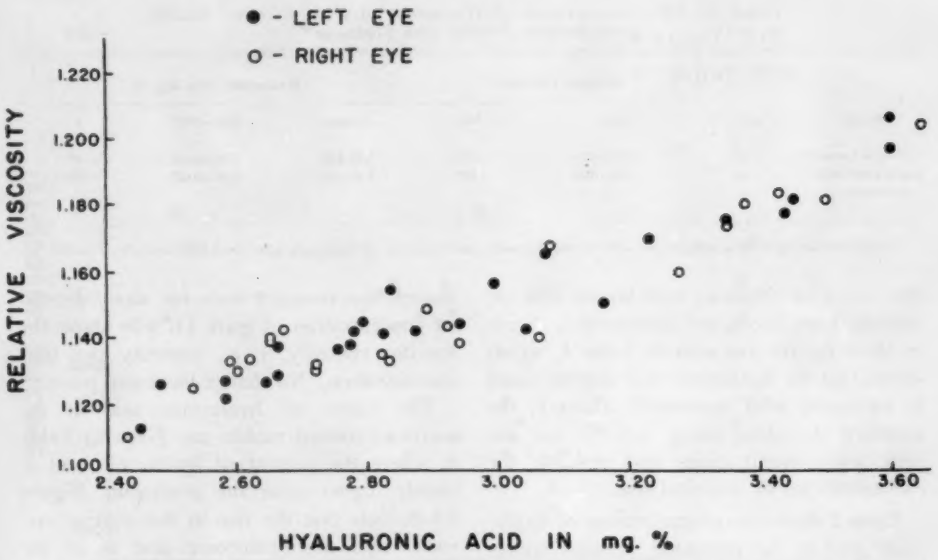


Fig. 1A.—Normal rabbits. The relationship between the relative viscosity and concentration of hyaluronic acid in the vitreous bodies. Left and right eyes compared.

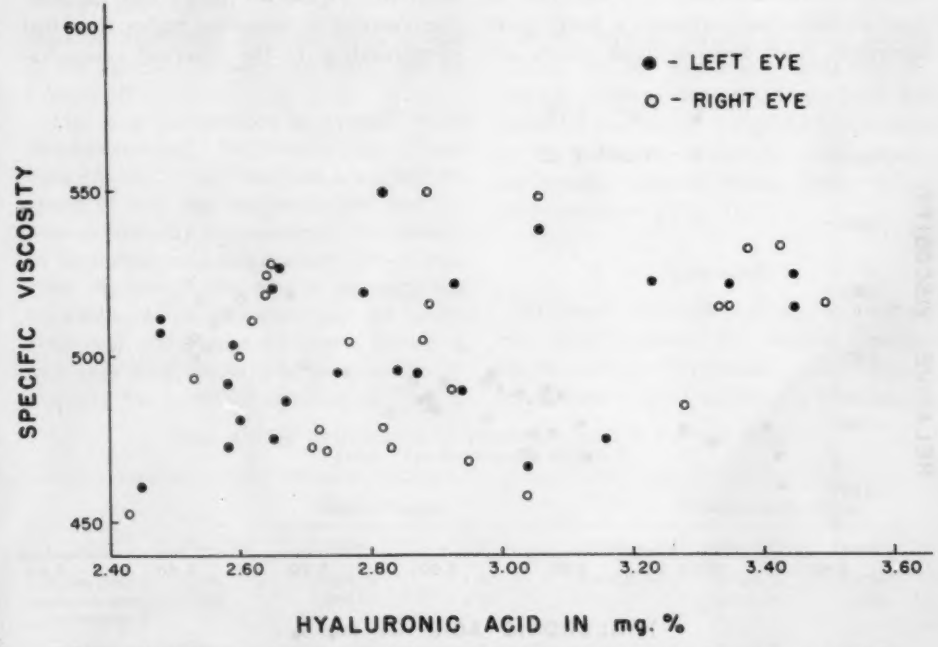


Fig. 1B.—Normal rabbits. The relationship between the specific viscosity and concentration of hyaluronic acid in vitreous bodies. Left and right eyes compared.

TABLE 3.—*The Concentration of Hyaluronic Acid in Vitreous Bodies from Rabbits Treated with Cortisone* *

| Group | Cases, No. | Relative Viscosity | | Hyaluronic Acid Mg. % | | |
|---|---|---|---|---|---|---|
| | | Range | *M* | Range | $M \pm \epsilon(M)$ | $\sigma$ |
| Left eyes (control) | 25 | 1.119-1.178 | 1.143 | 2.48-3.23 | 2.86±0.041 | 0.196 |
| Right eyes (after cortisone) | 25 | 1.128-1.209 | 1.168 | 2.87-3.67 | 3.31±0.039 | 0.193 |

* Differences between left and right eyes with regard to average concentration of hyaluronic acid. $D=0.4584$; $t=14.325$; $P=0.001$.

eral series of solutions with known concentrations were made and determined. Some of these figures are seen in Table 1, which shows that the hyaluronic acid content could be estimated with reasonable accuracy, the standard deviation being ±8.2% for the very low concentrations and ±4.2% for concentrations of practical use.

Table 2 shows the concentrations of hyaluronic acid in the untreated vitreous bodies of left and right eyes. Only small differences were observed in the same animal. Figure 1A represents the relationship between the relative viscosity and the hyaluronic acid concentration; it is seen that in spite of individual variations a fairly good agreement exists between these factors, although the viscosity does not alone depend on concentration. Figure 1B tells about the specific viscosity, i. e., viscosity per unit concentration. No change has taken place.

The values of hyaluronic acid in the cortisone-treated rabbits are given in Table 3, where the content of hyaluronic acid is clearly higher after the treatment. Figure 2A reveals that the rise in the relative viscosity and the hyaluronic acid is of the same order of size and, therefore, that the specific viscosity has remained unchanged.

In Table 4 (the thyroidectomized group) equivocal increase of the hyaluronic acid has occurred. Figure 3A shows that the relative viscosity is somewhat higher than that corresponding to the observed concentra-

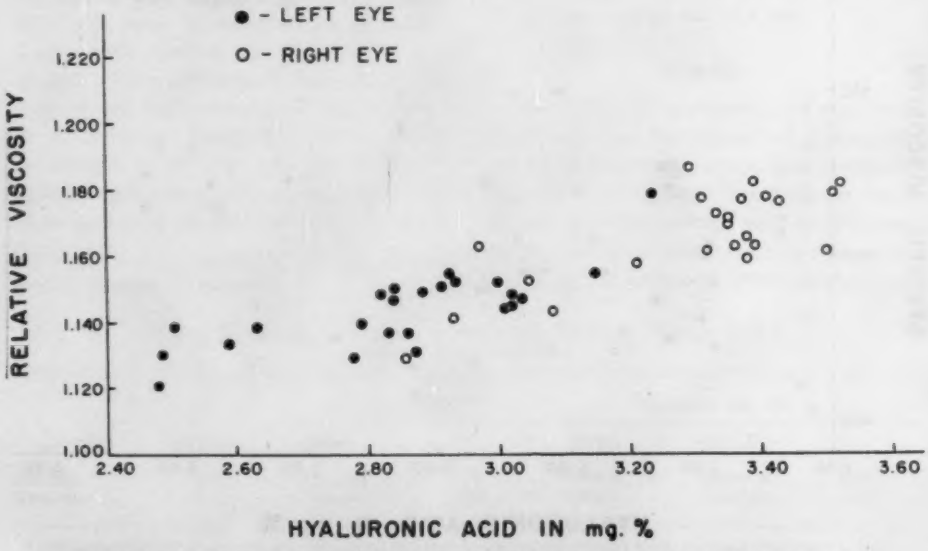


Fig. 2A.—Cortisone-treated rabbits. The relationship between the relative viscosity in the vitreous bodies. Left eyes (nontreated) compared with right eyes (treated).

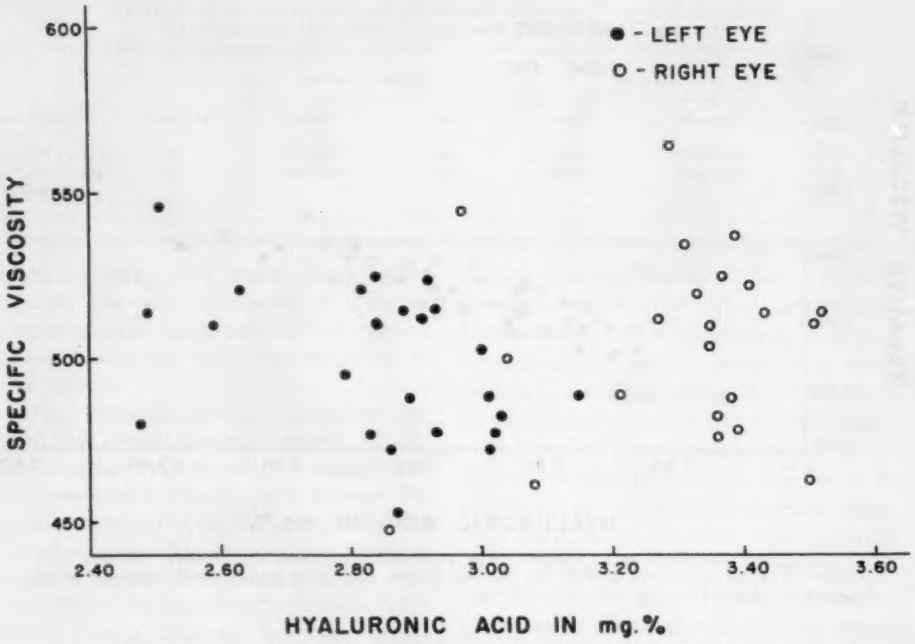


Fig. 2B.—Cortisone-treated rabbits. The relationship between the specific viscosity and concentration of hyaluronic acid in the vitreous bodies. Left eyes (nontreated) compared with right eyes (treated).

tions of hyaluronic acid, indicating a rise in the specific viscosity, as borne out by Figure 3B.

The same phenomenon is revealed in the thyroidectomized, thyrotropin-treated animals (Table 5), but this time a marked increase of both the hyaluronic acid and the relative viscosity has occurred, the content of hyaluronic acid being about 16% higher after treatment. The relative viscosity has increased considerably more than the hyaluronic acid, and Figure 4B shows, therefore, in a very conspicuous way that the specific viscosity has increased significantly.

In the thyroxin-treated group of rabbits (Table 6) the hyaluronic acid has decreased, whereas the relative viscosity has remained unchanged (Fig. 5A). Because of the decreased hyaluronic acid amount, the specific viscosity shows higher values after treatment (Fig. 5B).

## Comment

No linear relationship or proportionalism was found between the relative viscosity and the content of hyaluronic acid in vitreous taken from normal rabbits. A relationship

TABLE 4.—*The Concentration of Hyaluronic Acid in Vitreous Bodies from Thyroidectomized Rabbits* *

| Group | Cases, No. | Relative Viscosity | | Hyaluronic Acid, Mg. % | | |
|---|---|---|---|---|---|---|
| | | Range | *M* | Range | $M \pm \epsilon(M)$ | $\sigma$ |
| Left eyes (control) | 25 | 1.129-1.171 | 1.145 | 2.66-3.36 | 2.89±0.039 | 0.189 |
| Right eyes (after thyroidectomy) | 25 | 1.135-1.171 | 1.150 | 2.72-3.29 | 2.95±0.031 | 0.151 |

* Differences between left and right eyes with regard to average concentration of hyaluronic acid. $D=0.0624$; $t=2.1152$; $P=0.05$.

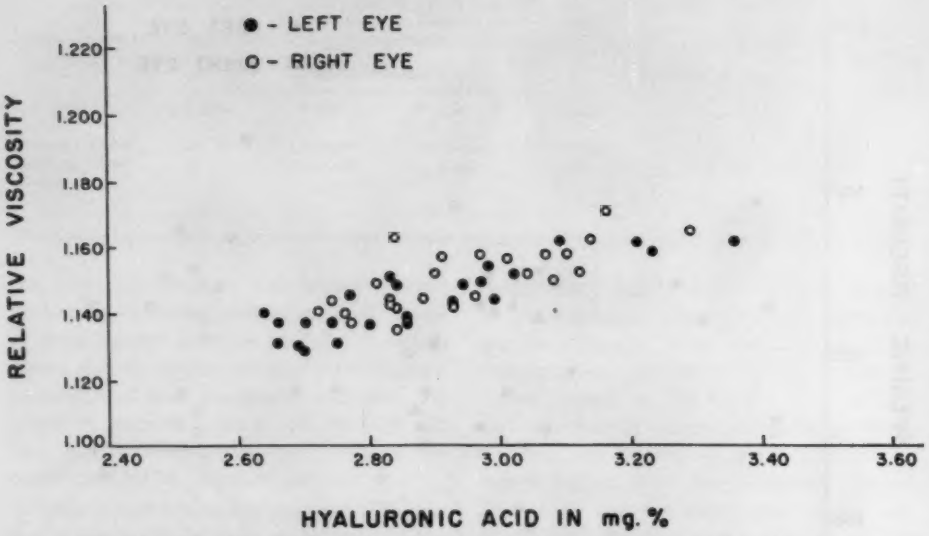


Fig. 3A.—Thyroidectomized rabbits. The relationship between the relative viscosity and concentration of hyaluronic acid in the vitreous bodies. Left eyes (nontreated) compared with right eyes (treated).

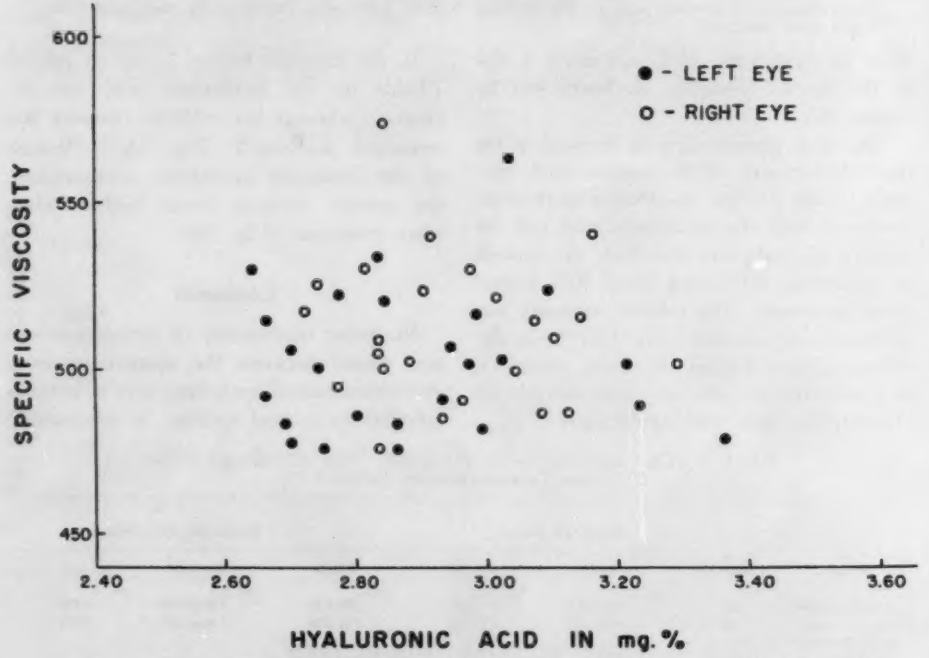


Fig. 3B.—Thyroidectomized rabbits. The relationship between the specific viscosity and concentration of hyaluronic acid in the vitreous bodies. Left eyes (nontreated) compared with right eyes (treated).

TABLE 5.—*The Concentration of Hyaluronic Acid in Vitreous Bodies from Thyroidectomized Rabbits Treated with Thyrotropic Hormone* *

| Group | Cases, No. | Relative Viscosity | | Hyaluronic Acid, Mg. % | | |
|---|---|---|---|---|---|---|
| | | Range | *M* | Range | $M \pm \epsilon(M)$ | $\sigma$ |
| Left eyes (control) | 30 | 1.122-1.151 | 1.144 | 2.53-3.45 | 2.90±0.051 | 0.274 |
| Right eyes (after treatment) | 30 | 1.163-1.243 | 1.190 | 3.00-3.95 | 3.36±0.044 | 0.236 |

* Differences between left and right eyes with regard to average concentration of hyaluronic acid. $D=0.4613$; $t=17.742$; $P=0.001$.

exists, however, in the respect that a higher viscosity generally corresponds to a higher concentration of hyaluronic acid, in spite of rather considerable individual variations in both factors.

After treatment various differences between the various groups occurred. Cortisone increased both the relative viscosity and the amount of hyaluronic acid, whereas the specific viscosity did not change significantly. Therefore, the higher relative viscosity might be explained as changes in the concentration of the hyaluronic acid alone. Very little is known, however, about the mechanism of action of cortisone on mucopolysaccharides. Histochemical studies by various authors (Asboe-Hansen 1950,[15] 1952 [16]; Cavallero and Braccini 1951,[17] and others) have indicated a decrease of extra- as well as intracellular mucopolysaccharides after treatment with cortisone, taking the reduction of the hyaluronidase-sensitive metachromasia of the ground substance of connective tissue and the mass of mast-cell granules as an expression of this change. Other investigations have shown, however, that cortisone causes an accumulation of mucopolysaccharides in the synovia and extracellular substance of retrobulbar connective tissues (Kulonen, 1951 [18]; Smelser and Ozanics, 1954,[19] 1955 [20]).

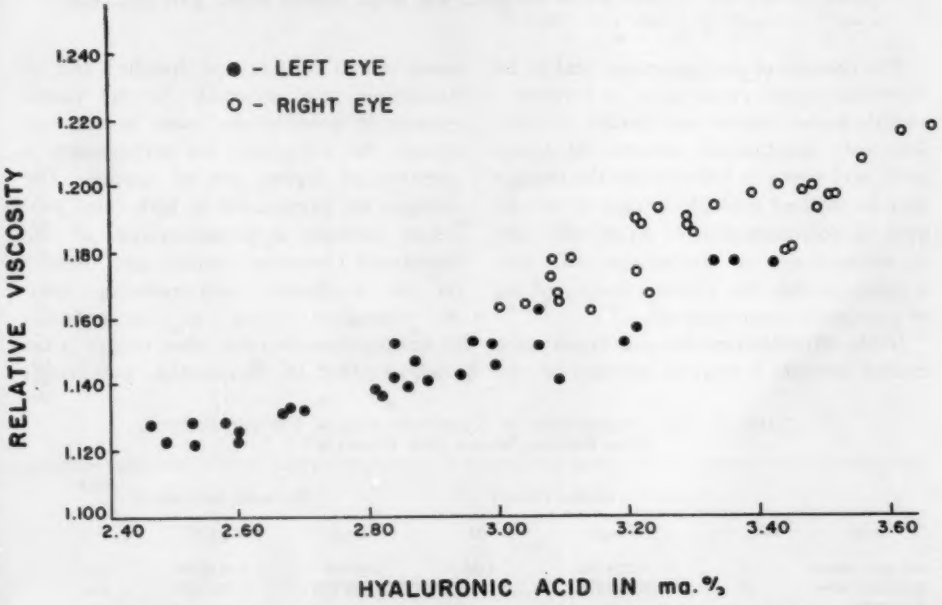


Fig. 4A.—Thyroidectomized rabbits treated with thyrotropin. The relationship between the relative viscosity and concentration of hyaluronic acid in the vitreous bodies. Left eyes (non-treated) compared with right eyes (treated).

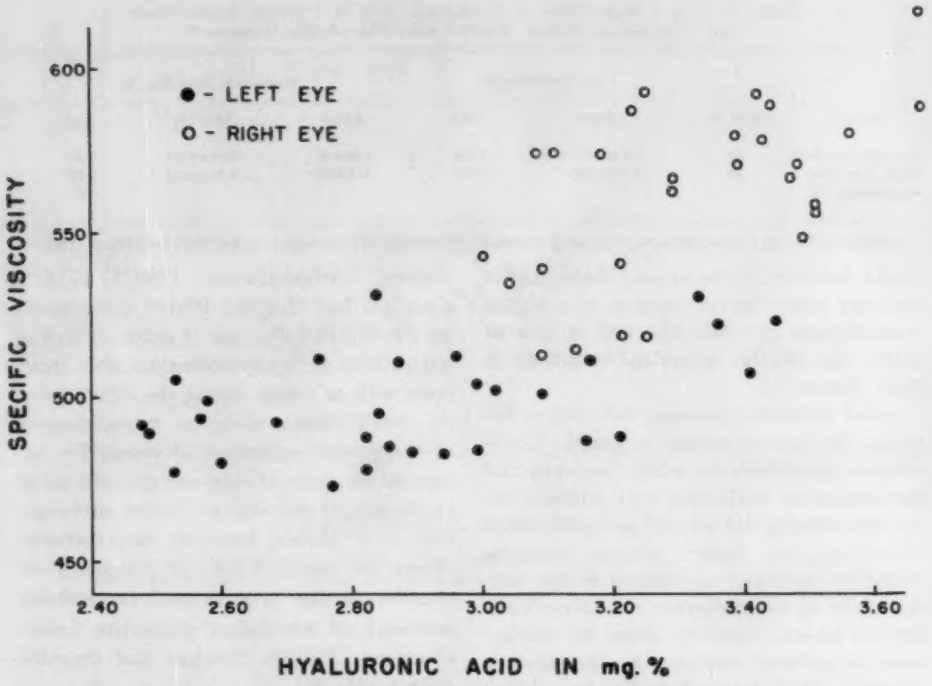


Fig. 4B.—Thyroidectomized rabbits treated with thyrotropin. The relationship between the specific viscosity and concentration of hyaluronic acid in the vitreous bodies. Left eyes (non-treated) compared with right eyes (treated).

The changes of the hyaluronic acid in the thyroidectomized group gave, as a result, a slightly higher relative and specific viscosity. The only questionable increase of hyaluronic acid seems to indicate that the changes may be induced through changes in the degree of polymerization of hyaluronic acid, its connections, or interactions with constituents within the vitreous body and not by changes in concentrations.

In the thyroidectomized and thyrotropin-treated animals a marked increase of viscosity (both relative and specific) and of hyaluronic acid occurred. As the pathogenesis is possibly the same in the two groups, the differences are perhaps only a question of degree, not of quality. The changes are presumably in both cases provoked through a preponderance of the thyrotropic hormone, which acts directly on the hyaluronic acid-producing cells. In connective tissue an accumulation of mucopolysaccharides also occurs after administration of thyrotropin, well-known

TABLE 6.—*The Concentration of Hyaluronic Acid in Vitreous Bodies from Rabbits Treated with Thyroxin* *

| Group | Cases, No. | Relative Viscosity | | Hyaluronic Acid, Mg. % | | |
|---|---|---|---|---|---|---|
| | | Range | $M$ | Range | $M \pm \epsilon(M)$ | $\sigma$ |
| Left eyes (control) | 27 | 1.127-1.166 | 1.145 | 2.49-3.28 | 2.92±0.036 | 0.181 |
| Right eyes (after treatment) | 27 | 1.131-1.169 | 1.144 | 2.48-3.11 | 2.78±0.038 | 0.191 |

* Differences between left and right eyes with regard to average hyaluronic acid concentration. $D=0.1378$; $t=6.557$; $P=0.001$.

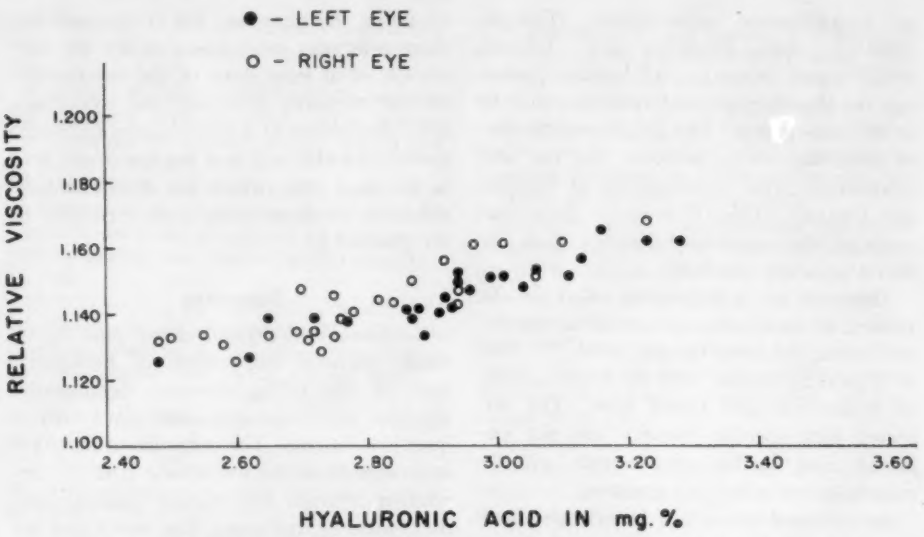


Fig. 5A.—Thyroxin-treated rabbits. The relationship between the relative viscosity and concentration of hyaluronic acid in the vitreous bodies. Left eyes (nontreated) compared with right eyes (treated).

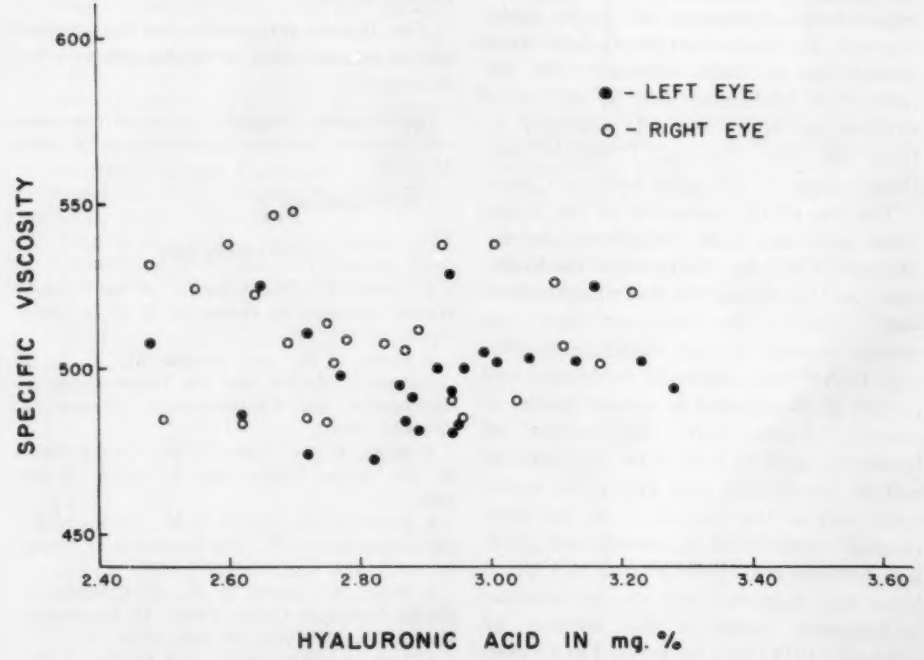


Fig. 5B.—Thyroxin-treated rabbits. The relationship between the specific viscosity and concentration of hyaluronic acid in the vitreous bodies. Left eyes (nontreated) compared with right eyes (treated).

in exophthalmos experiments (Dobyns, 1946[21]; Asboe-Hansen and Iversen, 1952,[22] and others). In human pathology the thyrohypophyseal syndrome may be of the same origin. The detailed mechanism of exophthalmos is, however, still not well established. The investigations of Smelser and Ozanics (1955)[20] seem to show that more of the pituitary hormones than the thyrotropin are involved.

Thyroxin has a decreasing effect on the amount of mucopolysaccharides in connective tissue (Asboe-Hansen, 1950).[23] This is in good agreement with the lower content of hyaluronic acid found here. The observed high specific viscosity was not expected, and further experiments will be undertaken to solve this problem.

As indicated above, our knowledge about hormonal effects on mucopolysaccharides is still rather fragmentary. The same thing may also be applied to the chemical structure and composition of hyaluronic acid in the vitreous body. This is even truer in regard to the hyaluronic acid in the rabbit vitreous, as most experiments have been carried out on cattle vitreous. The low content of hyaluronic acid in the rabbit vitreous has been observed previously by Boruchoff and Woodin (1956),[24] who found values on the same level as I have.

The site of the formation of the hyaluronic acid has been considered before. Meyer (1938)[5] has claimed that the hyaluronic acid is formed by the ciliary epithelium. This is, however, not likely for several reasons. Recent experiments (Balazs, 1956)[25] have shown no hyaluronic acid present in the aqueous in various species of animals. Furthermore, the content of hyaluronic acid is highest in the posterior half of the vitreous, and, finally, the hyaluronic acid of the vitreous is so far most naturally considered a mesodermal product. Schweer et al. (1956)[26] have in a speculative way suggested that the protoplasmic prolongation found in the vitreous by Schwarz (1951) may be involved in a hyaluronic acid-forming process. Balazs (1957)[27] has recently described granulated cells surrounding the vitreous. He points out that these cells may be responsible for the formation of at least some of the constituents of the vitreous, including the hyaluronic acid. According to Asboe-Hansen (1950),[28] another possible origin of the hyaluronic acid is the mast cells, which are found in considerable numbers in the uvea, especially in the choroid.‡

## Summary

Cortisone and thyroidectomy plus thyrotropin increase the content of hyaluronic acid of the rabbit vitreous significantly, whereas thyroidectomy alone gives only a questionable rise. The response to thyroxin is a decrease of the hyaluronic acid. A correlation between the relative viscosity and the content of hyaluronic acid shows that the specific viscosity remains unchanged in the cortisone-treated group but is increased in the thyroidectomized, thyroidectomized and thyrotropin-treated, and thyroxin-treated animals.

The factors responsible for the changes of the concentration of hyaluronic acid are discussed.

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‡ To be published.

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# Multiple Targets in Visual Field Examinations with a Tangent Screen

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It is my purpose to describe simple and practical techniques which make it possible to diagnose early hemianopic defects and relative central scotomas which might be missed with standard methods. These new techniques also contribute evidence that the phrase "macular sparing" is a misnomer.

The use of more than one target to stimulate different positions of the retina simultaneously has been limited mainly to the study of the phenomenon of "extinction." * Multiple targets have been used in the Harrington-Flocks [2] tachystoscopic screener, but to my knowledge no one has used multiple targets with the conventional tangent screen in the manner I shall describe.

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From the Department of Ophthalmology, University of Oregon Medical School.

* "Extinction" is defined by Bender and Krieger [1] as "a condition wherein the simultaneous introduction of two stimuli into a sensory field results in the subjective disappearance of one of the stimuli."

Conventional single-target testing requires only a "present" or "absent" type of response. Use of multiple targets allows a patient to make a comparison of brightness and therefore is more delicate. At the same time, it is easier for the patient and the examiner to decide whether a field defect is present.

One technique of using multiple targets is as follows: The patient is asked to fixate the fixation point of the conventional tangent screen (I prefer a 2 meter screen, but a 1 meter screen can be used) in the usual manner. The eyes are tested separately, but in homonymous hemianopia binocular testing can be done. A device carrying two targets of equal size is brought from above, with the two targets kept at equal distance from the vertical meridian of the screen (Figs. 1 and 2). As the targets are brought down, the patient is asked to state when he first sees one or two targets. If two targets are seen at the same moment, the response is normal. Slight differences (1 degree) in

Figure 1

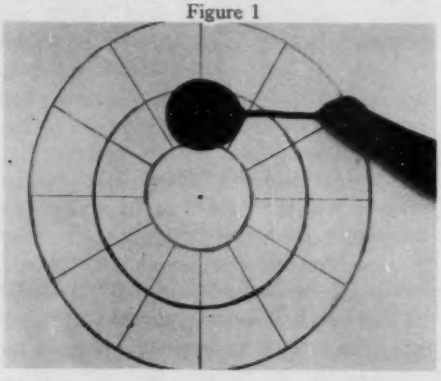

Fig. 1.—Here a paddle with two test objects is used. The paddle is a wire frame covered with the same type of black felt as is used for the tangent screen. Berens type test objects can easily be pinned into the felt. The examiner wears a black sleeve to reduce distracting contrasts. The size of the targets used will vary with the visual acuity of the patient being tested. For routine work 3 mm. white targets work well.

Figure 2

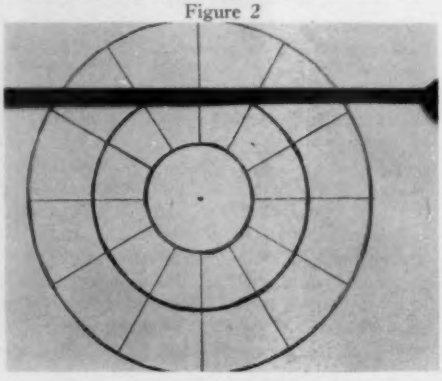

Fig. 2.—Here a felt-covered stick is used to carry the targets. The targets can be placed to stimulate more peripheral portions of the retina.

the level at which the targets are seen are usually not important, but experience with the method rapidly indicates the range of normal. Once the targets are seen, they are brought down a little farther and the patient is asked if one is definitely brighter than the other. This technique sometimes detects relative field defects not found with even the most detailed single-target techniques. The same procedure is repeated with the targets being brought into the inferior field from below.

Another method of using multiple targets was suggested by Bay.[3] The two targets are brought into the seeing area and kept stationary. The targets will fade from view unless they are rather large; however, the target on the abnormal side will fade first. Here, experience with the technique will establish normal patterns of response. Using this technique in the central 2 to 10 degrees, Bay was able to show that even in cases of so-called macular sparing the involved side had reduced function. I have repeatedly checked this in my cases and have found this to be true. I believe that the existence of true macular sparing (a normally functioning central area) must be unusual. The clinical concept of macular sparing as an aid to localizing lesions is still useful, but I believe that it is incorrect to think that the macular fibers or the visual cortex serving the macular region are not involved in the pathological process. With conventional single-target testing macular sparing can readily be found no matter how accurately fixation is controlled. However, with the use of multiple targets it can usually be shown that reduced function is present on the "spared" side; that is, the "spared" macula really is not "spared."

Multiple targets can be used to detect slight depression of the central field. Suitable targets (the size depends on the visual acuity) are placed at fixation and at about 3 to 5 degrees from fixation (Fig. 3). The patient is asked to state which of the two is brighter and then which fades first. The central target should be brighter and usually will not fade in normal persons. Multiple

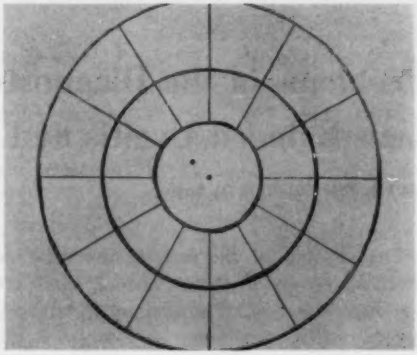

Fig. 3.—No carriers are used for this type of stimulation. The targets are pinned to the screen. Sometimes white targets will yield more accurate responses than red, but color targets definitely are valuable.

colored targets (especially red) will bring out small central defects missed with ordinary single-target techniques. Obviously, a patient who has a centrocecal scotoma may give confusing responses; however, if the target that is placed eccentrically is put on the side opposite the blind spot no confusion will result.

## Summary

Methods of detecting minimal hemianopic defects and central defects are described. The use of multiple targets will often detect early pathology missed when single targets are used. The use of multiple targets in the central region tends to indicate that so-called macular sparing does not really exist.

The use of paddles to carry targets in tangent screen work was first suggested to me by Dr. Max Chamblin several years ago. To my knowledge, however, he has not used more than one target on the paddle.

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# Problems in the Diagnosis and Treatment of Lens-Induced Uveitis and Glaucoma

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The capsule of the lens is normally an effective barrier to the escape of lens protein into the eye. Under certain circumstances, however, lens matter is found outside the capsular barrier.

Thus, in certain hypermature cataracts the lens may appear to be grossly intact but lens matter appears clinically to have escaped through the capsule. After extracapsular extraction or after trauma to the lens capsule, lens matter is freely exposed to the intraocular fluids. Hypermature cataracts have been known to shrink and eventually absorb without causing any inflammatory response in the eye. Likewise, in the majority of cases of extracapsular extraction residual lens cortex absorbs without the occurrence of any undue reaction. In some cases a mild inflammatory response occurs which subsides when the lens cortex is absorbed.

In the occasional case, however, exposure of free lens matter to the intraocular fluids evokes an inflammatory response of great severity, so prolonged that the eye may eventually be lost if the residual lens matter is not removed.

Prior to the classical paper of Verhoeff and Lemoine,[1] in 1922, one finds in the literature only a few references[2-4] to the possibility of lens-induced ocular inflammation. By means of clinical case reports, pathologic examination of enucleated eyes and tests for skin sensitivity to lens protein, Verhoeff and Lemoine established the entity to which they gave the name "endophthalmitis phacoanaphylactica." These authors also mentioned the toxic effects of lens protein from hypermature cataract.

Since that time, several authors have reported the curative effect of lens extraction in cases of hypermature cataract with severe uveitis and glaucoma.[5-8,17] Pathologic studies on eyes with hypermature cataract enucleated because of intractable uveitis and glaucoma have been reported by Verhoeff and Lemoine,[1] Courtney,[5] deVeer,[9-11] Irvine and Irvine,[6] Law,[12] and Morgan.[15] In these reports the pathologic findings were typical of lens-induced uveitis. Pathologic specimens showing both endophthalmitis phacoanaphylactica and sympathetic ophthalmia have also been reported.[6,9] Many eyes enucleated with a diagnosis of sympathetic ophthalmia, on pathologic examination, revealed only lens reaction and no evidence of sympathetic ophthalmia. In some cases, actually diagnosed as sympathetic ophthalmia, a careful study of the pathologic report reveals that the findings were more typical of lens reaction than of sympathetic ophthalmia.[14,16] In others, though true sympathetic ophthalmia existed, typical lens reaction was also present.[6,13-15] deVeer[10] has conjectured that in some cases there may be a causal relation between lens-induced uveitis and sympathetic uveitis.

In the excellent paper by Irvine and Irvine[6] the pathology of the various types of lens reaction is reported and the summaries of case reports illustrate the consequences of failure to diagnose and properly treat the condition, as well as the dramatic cure effected when the offending lens or residual lens matter is removed in time.

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In the present communication a series of case reports is given to illustrate further the clinical features of lens-induced reactions of various types and in various stages, the unfavorable results of errors in diagnosis and management, and the favorable results of early and proper treatment.

The need for such a report is evident in the large number of eyes which come to the pathologic laboratory showing lens reaction and the considerable number seen clinically that are being treated for nonspecific uveitis in which lens matter as the cause of the inflammation is unrecognized. It would also appear that lens-induced uveitis and glaucoma from a hypermature cataract in the vitreous has not heretofore been reported. Nor is it evident that adequate consideration has been given to the removal of lens substance as a therapeutic measure in cases of prolonged inflammation in connection with traumatic cataract and after extracapsular cataract extraction.

Tests for skin sensitivity to lens protein have not been made in any of the cases here reported. Such tests are not invariably reliable, since typical cases of lens reaction have been reported in which skin tests were negative.[7] For practical purposes, I believe the diagnosis of lens-induced uveitis can be made on purely clinical grounds. In this communication no attempt has been made to classify the cases into various types of lens-induced reaction. This has been adequately done on a pathologic basis by Irvine and Irvine.[6] Whatever the classification in a given case, the important thing is to recognize that the lens or residual lens matter is the cause of the inflammation and that removal of the lens or residual lens matter is the most important factor in the relief of the trouble.

## Report of Cases

CASE 1.—Hypermature cataract, uveitis, and glaucoma. Normal anterior chamber. Intracapsular extraction with relief of the glaucoma and uveitis. Man, aged 77.

Intracapsular cataract extraction was performed on the right eye in 1941. Convalescence was uneventful. Corrected vision was 6/6. In 1943 cataract in the left eye was hypermature. On Oct. 16, 1948, there were redness and pain in the left eye. Atropine was prescribed by a physician. On Oct. 18, 1948, there were moderate congestion and a posterior synechia at 9 o'clock. There were many cells in the aqueous. Tension was normal to palpation. On Oct. 22, 1948, there were moderate congestion, slight epithelial edema, and many cells in the aqueous. Tension was 40 mm. Light projection was faulty nasally and accurate elsewhere.

On Oct. 23, 1948, intracapsular cataract extraction was performed on the left eye. Convalescence was uneventful. Final corrected vision was 6/9.

*Comment.*—This case is typical of uveitis and glaucoma caused by a hypermature cataract in an eye with a normal anterior chamber. Lens extraction in such cases invariably results in relief of the uveitis and glaucoma.

CASE 2.—Severe purulent endophthalmitis and glaucoma secondary to hypermature cataract. Dramatic subsidence of the uveitis and glaucoma after lens extraction, with recovery of good vision. Woman, aged 73.

The patient was first examined on June 29, 1957. There was a history of cataract extraction on the right eye 10 years previously. The convalescence was stormy, and the eye never recovered good vision. Vision had been very poor in the left eye for five years. The left eye had been inflamed and painful for four days.

The right eye was quiet. Corrected vision was 5/200. The pupil was somewhat drawn up. The vitreous showed many opacities. The disc was normal. Retinal vessels appeared attenuated. Tension was 20 mm.

The left eye showed marked congestion and chemosis of the conjunctiva. The cornea was edematous throughout. The pupil was semidilated. There were a hypermature cataract and a marked aqueous flare. The tension was 52 mm.

Prednisone, acetazolamide (Diamox), and antibiotics were given systemically; miotics and antibiotics, locally. During the next three days tension ranged from 35 to 52 mm. The chemosis became more marked. A purulent exudate developed in the anterior chamber and steadily increased until on July 3, three days after admission, the iris could scarcely be seen. The anterior chamber appeared to be almost completely filled with pus.

On July 3, 1957, an intracapsular cataract extraction was done, without complication. The eye began to improve immediately after operation, and the patient was discharged on the 12th postoperative day, with the eye much whiter.

On July 20, 1957, five days after discharge, there was only slight congestion. The vitreous was somewhat hazy. Vision with glass was 6/60.

Further convalescence was uneventful, and when last examined, on Sept. 25, 1957, the eye was white and quiet; tension, normal. Corrected vision was 6/9.

*Comment.*—This case illustrates the most marked lens reaction we have seen. The immediate preoperative appearance was much like panophthalmitis. Since under antibiotic and steroid therapy the condition steadily became worse, it was decided to remove the lens. The dramatic response to the removal of the hypermature cataract indicated that the lens was entirely responsible for the violent inflammation.

CASE 3.—Spontaneous posterior dislocation of both lenses 20 years previously. Severe uveitis with hypopyon in the right eye which did not respond to medical treatment. Incomplete removal of the lens resulting in phthisis bulbi. Uveitis and glaucoma in the remaining eye, which subsided, and the eye remained quiet for several months following peripheral iridotomy and local and systemic steroid therapy. Recurrence of severe glaucoma which could not be controlled medically. Eventual appearance of lens matter in the anterior chamber. Removal of a ruptured hypermature cataract from the vitreous. Dramatic subsidence of the inflammation and the glaucoma, with recovery of 6/9 vision.

A woman, aged 50, was first seen in consultation on Dec. 15, 1954. There was a history of wearing cataract glasses for 20 years. For three months there had been redness and loss of vision in the right eye. The patient's ophthalmologist reported that when she was first seen, in September, 1954, the right eye showed exudates in the anterior chamber, considerable redness, and a tension of 60 mm. She was treated with local and systemic steroids, acetazolamide, miotics, and later atropine. For a while the eye improved, and then it became worse again. When the patient was first examined by me, the right eye showed considerable congestion. The cornea showed epithelial edema. The anterior chamber was normal in depth. There was 2 mm. of hypopyon. The lens was not in situ and could not be seen. The pupil was 2 mm. in diameter. There was no red reflex. Tension was 16 mm. An attempt to remove the dislocated lens was advised. This was attempted later, and some lens fragments were said to be looped out, but the eye subsequently became phthisical and totally blind.

At the time of this examination the left eye was quiet. A cataractous lens could be seen in the lower vitreous. Tension was 22 mm. Vision with a cataract glass equaled 6/9.

The patient was next seen on May 12, 1956, with a history of pain and loss of vision for two days. The eye was congested. The cornea showed epithelial edema. Some vitreous strands could be seen in the pupillary area and just anterior to the pupil. The white cataractous lens was in the lower vitreous. The disc was normal. Tension was 90 mm. Acetazolamide and mydriatic drugs were prescribed. The following morning tension was 46 mm. Gonioscopy showed for the most part a wide-open angle. In places the attachment of the iris root seemed to encroach somewhat on the trabecular meshwork. Two days later the tension

was 65 mm. On May 16, 1956, a peripheral iridotomy was done above, on the theory that vitreous in the anterior chamber might be blocking the angle. No definite vitreous strands were visible in the anterior chamber, but a few cells could be seen to tremble on motion of the eye. After the iridotomy tension remained at normal levels; treatment with acetazolamide and local steroids was gradually reduced. By November, 1956, all treatment had been discontinued except instillation of 2% pilocarpine four times a day. During the next six months the highest tension recorded was 27 mm. and vision with correction was 6/9.

On May 4, 1957, vision began to be blurred. When seen on May 5, 1957, the eye showed minimal congestion. There were many cells in the aqueous. The cornea was steamy. The tension was 65 mm. The patient was admitted to the hospital. Acetazolamide was prescribed. The following morning tension was 15 mm. Gonioscopy showed an open angle as before. At 6 o'clock and at 3 o'clock there was whitish material on the corneoscleral meshwork which did not look like exudate, and between 4 and 6 o'clock there were precipitates on the meshwork. During the next 10 days tension stayed at a low level and there were many folds in the cornea. Vision was reduced to hand movements. Tension then rose and remained 40 to 50 mm. On June 3, 1957, four weeks after admission, grayish material was visible in the bottom of the anterior chamber which on slit-lamp examination looked fluffy and resembled lens material. This increased in amount each day, and on June 8, 1957, an operation was performed. A full cataract section was made. After the section a considerable quantity of fluid escaped and the eye collapsed. An iridectomy and inferior iridotomy were done. A faint glow with the ultraviolet light deep in the vitreous chamber indicated the presence of the lens, but it could not be seen clearly. The vitreous chamber was irrigated with saline, and the lens immediately presented in the wound and was delivered. It was a large hypermature lens, ruptured on one side, with flocculent lens matter extruding. Multiple sutures were employed to close the wound, and the eye was filled with saline. For some time after the operation the cornea remained edematous. On the patient's discharge from the hospital, June 23, 1957, the eye showed very little congestion. Tension was normal. The vitreous was clear; the fundus was normal except for a few hemorrhages in the macula. The condition of the eye steadily improved, and on July 12, five weeks after operation, all treatment was discontinued. The retinal hemorrhages gradually absorbed. The eye remained white and quiet and symptom-free, with normal tension. When the patient was last seen, five months after lens extraction, vision with glass equaled 6/9; tension, 20 mm.

*Comment.*—All evidence points to the fact that the inflammation in the right eye was due to lens reaction and that the eye was lost as a result of late and incomplete removal of the lens. The flare-up in the left eye in May, 1956, may have been due to lens reaction, partly relieved by opening the anterior chamber and employing steroid therapy.

During the last flare-up, after an initial lowering of tension with acetazolamide, tension rose and could no longer be controlled. One month after the flare-up, what appeared to be flocculent lens material was visible for the first time in the anterior chamber. This indicated that in all probability lens reaction was the cause of the difficulty, and it was felt that heroic measures were justified in an attempt to remove the lens. Actually, since the vitreous was completly fluid, the lens was delivered very easily by irrigation of the vitreous chamber. The dramatic relief of the inflammatory process and of the glaucoma indicates that the ruptured hypermature cataract in the vitreous chamber was the cause of the difficulty.

CASE 4.—Extracapsular extraction on the left eye. Considerable postoperative reaction, but the eye was quiet, and vision was 6/12 ten weeks after operation. Immature

cataract in the right eye, vision 6/15. Seven months after operation on the left eye, the right eye became inflamed. There were many heavy mutton-fat keratic precipitates and many cells in the aqueous. Local treatment with steroids and atropine was ineffective. After six months tension became elevated; the cataract was still immature. Intracapsular cataract extraction was followed by rapid subsidence of the uveitis and glaucoma. Recovery of useful vision.

A man, aged 64, was first examined Dec. 2, 1953. There was an immature cataract in the right eye, vision 6/15. There was a mature cataract in the left eye. Extracapsular cataract extraction was done on the left eye, Jan. 7, 1954. The postoperative course was stormy, but on March 24, 1954, the eye was quiet and vision with correction was 6/12.

On Aug. 4, 1954, the patient returned to the clinic with a history of redness and pain in the right eye of six weeks' duration. Examination revealed considerable congestion, many mutton-fat keratic precipitates, many cells in the aqueous, normal tension, and vision of 6/30. Scopolamine and 2.5% hydrocortisone were prescribed. During the next six months the patient was seen at one- to three-week intervals. At all visits the eye was more or less congested and many keratic precipitates and cells were noted.

On Jan. 12, 1955, tension in the right eye was 30 mm.

On Feb. 23, 1955, tension was 50 mm. and the uveitis was still active. The cataract was still immature. Vision equaled counting fingers at 3 ft. Gonioscopy showed an open angle.

On March 3, 1955, an intracapsular cataract extraction was done. The patient was discharged on the sixth postoperative day.

On March 16, 1955, there was slight congestion; no keratic precipitates were noted.

On March 30, 1955, the eye was quiet; there were no cells or keratic precipitates.

On April 6, 1955, the eye was quiet; there were no keratic precipitates; three or four cells were noted in the aqueous. From this time on the eye remained quiet and symptom-free, with normal tension. Corrected vision was 6/18, owing to macular degeneration. A secondary membrane developed in the left eye, which was needled on Jan. 19, 1956. The patient was last examined on April 25, 1956. Both eyes were quiet; tension was 12 mm. in each eye. Corrected vision was right 6/15, left 6/18.

*Comment.*—It has been generally understood that a cataract must be mature or hypermature to cause lens-induced uveitis and glaucoma. The fact that the severe uveitis in this case continued unabated for six months during local treatment and subsided dramatically after intracapsular removal of the lens is strong indication that the uveitis was induced by the lens, even though the cataract was still immature at the time of extraction.

CASE 5.—Traumatic cataract from perforating wound of the cornea and anterior lens capsule. Repair of the corneal wound. Complete traumatic cataract. Three months later the eye was red and painful; tension, 22 mm.; there were large mutton-fat keratic precipitates on the lower cornea. Linear cataract extraction. Rapid subsidence of all inflammatory signs. Ultimate vision 6/12 with correction.

This patient was first examined on April 21, 1946. On that date an explosion of a glass bottle resulted in a perforating wound of the cornea and lens in the left eye. The corneal wound was sutured. A mature cataract was evident in the immediate postoperative period. Six weeks postoperatively the eye was white and quiet. Three months postoperatively the left eye was red and painful; there were large mutton-fat keratic precipitates on the lower cornea; tension was 22 mm.

On Aug. 9, 1946, an operation was performed. Iridectomy, inferior iridotomy, and linear cataract extraction were done. Typhoid vaccine was given intravenously three and again five days postoperatively. Convalescence was uneventful.

On Sept. 3, 1946, the eye was mildly congested. There were no keratic precipitates.

On Sept. 19 there was still slight redness.

On Oct. 31, 1946, the eye was quiet; there was a faint aqueous flare.

On Nov. 16, 1946, the eye was white and quiet. There were no cells in the anterior chamber and no flare.

Since that time the eye has remained white and quiet. Vision with a cataract glass is 6/12.

*Comment.*—Three months after a perforating wound of the cornea and lens with traumatic cataract the eye became red and irritable, with heavy mutton-fat keratic precipitates on the lower cornea. After linear extraction the inflammation rapidly subsided, and it has not recurred. The heavy mutton-fat keratic precipitates on the cornea suggested lens reaction. The rapid subsidence of inflammatory signs after extraction of the lens indicates that lens reaction was the correct diagnosis, and the complete relief of the inflammation following lens extraction confirms the diagnosis.

CASE 6.—Extracapsular extraction with considerable retained cortex. Severe postoperative uveitis and glaucoma favorably influenced by intravenous typhoid therapy six weeks after operation. Gradual subsidence of the uveitis and glaucoma over a period of five months, with recovery of good vision.

A woman, aged 75, had an uneventful intracapsular extraction on the right eye in 1949.

On Feb. 15, 1950, extracapsular extraction was performed on the left eye. There was considerable residual cortex. Postoperatively the eye remained red and irritable. One month after operation there was a marked aqueous flare; there were many cells in the anterior chamber; the cornea was studded with precipitates, and tension was elevated.

Six weeks after operation typhoid vaccine was given intravenously three times at 48-hour intervals, with a good febrile response. The eye became much whiter; aqueous cells and keratic precipitates lessened considerably, but the tension remained somewhat elevated. During the next three months the uveitis gradually subsided and tension returned to normal levels.

On Oct. 10, 1950, the eye was white and quiet; tension, 22 mm.; corrected vision, 6/18. Three months later corrected vision was 6/12, and on July 24, 1951, one and one-half years after operation, corrected vision was 6/9.

*Comment.*—This case is an illustration of a severe uveitis with glaucoma due to lens reaction which under conservative therapy gradually subsided over a period of several months as the residual cortex was absorbed, with a good functional result in the end. Intravenous typhoid therapy apparently had a very beneficial effect in reducing the inflammation. It seems probable that the convalescence could have been considerably shortened if the residual lens cortex had been removed when it became obvious that it was the cause of the inflammation.

CASE 7.—Extracapsular extraction with considerable residual lens cortex. Severe postoperative uveitis. Removal of residual lens cortex two months after cataract extraction, with dramatic subsidence of the uveitis. Recovery of useful vision.

A man, aged 73, was first seen April 29, 1957. There was immature nuclear cataract in each eye, with a vision of 6/60.

On May 5, 1957, an extracapsular cataract extraction was done on the left eye. Postoperatively it was evident that considerable cortical material remained, and the eye was inflamed and painful.

On June 19, 1957, the eye showed considerable congestion. There was considerable cortical material in the anterior chamber, and there were many keratic precipitates on the cornea. Tension was normal.

On July 12, 1957, an operation was done. A keratome incision was made, and considerable cortical material was removed by irrigating the anterior chamber.

By July 25 the eye was practically white. There was a slight aqueous flare, but there were no keratic precipitates on the cornea. The vitreous was hazy.

On Aug. 26, 1957, the eye was white and quiet. There was moderate vitreous haze. Vision was 6/60.

On Sept. 28, 1957, the eye was white and quiet. The anterior face of the hyaloid was thickened. Corrected vision was 6/18.

*Comment.*—This case illustrates the wisdom of prompt removal of retained cortex when there is clear evidence of lens reaction. The eye quieted promptly and has useful vision. Had removal of the residual lens cortex been deferred, the serious consequences of prolonged inflammation illustrated in Cases 8 to 12 might well have ensued.

Case 8.—Extracapsular extraction with considerable residual cortex. Prolonged postoperative uveitis with moderate elevation of tension. Removal of residual cortex seven months after operation, with marked improvement in the uveitis. One and one-half years after operation the eye still shows mild injection periodically; tension is readily controlled by medical means. Poor functional result.

A woman, aged 52, was first seen on Aug. 10, 1956. There was a history of extracapsular cataract extraction on the left eye for intumescent cataract on April 13, 1956. A discission was done in May, 1956. Ten days after the cataract extraction tension was 45 mm. Since that time the eye has been inflamed and tension has ranged from normal to 45 mm. Local treatment has consisted of isoflurophate (DFP) and steroid therapy.

Examination. The right eye was normal except for myopia. The left showed slight congestion, old keratic precipitates on the back of the cornea, and considerable capsular and cortical remains in the pupil. There were many posterior synechias. Gonioscopically the angle was open in two-thirds of its extent. Vision equaled hand movements. Tension was 12 mm.

During the next three months the eye became more inflamed, there were many keratic precipitates on the cornea, and tension was usually high normal.

When the patient was examined on Nov. 8, 1956, the left eye showed moderate ciliary congestion and many keratic precipitates on the cornea, with edema over the area of greatest deposition of keratic precipitates. Vision equaled accurate light projection. Tension was 19 mm.

On Nov. 19, 1956, an operation was performed. A limbal section of the upper third of the circumference of the cornea was made. Both iris pillars were excised; the capsular and cortical remains were separated from the iris with a spatula. An inferior iridotomy was done. The mass of capsular and cortical material was removed with forceps, and the anterior chamber was irrigated. Postoperatively the eye whitened rapidly. Corneal edema of the upper half of the cornea persisted for some time, but it eventually subsided except for 2 or 3 mm. adjacent to the upper limbus.

In June, 1957, the eye was white and quiet. Tension was 17 mm. Vision with correction was 6/60. There was some thickening of the hyaloid. The fundus showed no gross pathology.

In the period from June, 1957, to January, 1958, the eye was usually quiet, but at times it showed a slight blush. When last examined, in January, 1958, the eye was quiet and tension was normal. There was some opacity in the upper part of the cornea, and there was an inflammatory membrane in the upper part of the coloboma. Vision was 6/60.

*Comment.*—That this prolonged postoperative uveitis was due to retained lens cortex is indicated by the striking improvement following removal of the lens matter. The fact that the eye one and one-half years after the initial operation still showed mild inflammation at times suggests that there may still be a small amount of lens matter remaining in the eye. Fortunately, the angle remained largely open throughout the period

of inflammation and glaucoma was never a serious problem.

CASE 9.—Extracapsular cataract extraction followed by prolonged severe uveitis and glaucoma. Immature cataract in the fellow eye with open-angle glaucoma controlled by miotics. Removal of residual lens cortex seven months after the cataract extraction, with prompt subsidence of the inflammation. Control of the residual glaucoma due to peripheral anterior synechias by cyclodiathermy and medical treatment. Ultimate vision, counting fingers at 5 ft. Intracapsular cataract extraction on the fellow eye, with uncomplicated recovery.

A woman, aged 68, was first seen on July 9, 1956, with a history of having had a cataract extraction on the right eye seven months previously. The eye has been continuously inflamed and painful since that time.

Right eye: Tension was 67 mm. The eye was markedly inflamed. The cornea showed epithelial edema throughout. There was a faint red reflex. There were remnants of capsule and lens cortex at the edges of the coloboma. Gonioscopy was not possible, because of the cloudy cornea.

Left eye: Tension was 50 mm. There was slight congestion. The cornea was clear; anterior chamber, normal. There were no keratic precipitates, cells, or flare. There was an immature anterior and posterior cortical cataract. Corrected vision was 6/15. Gonioscopy showed an open normal-appearing angle.

The patient was admitted to the hospital, where she was given prednisone and acetazolamide by mouth and hydrocortisone and atropine locally in the right eye and 4% pilocarpine in the left. Two days later tension was right 45 mm., left 20 mm.

On July 12, 1956, an operation was performed on the right eye. Through a keratome incision considerable cortical material was irrigated out of the anterior chamber. Acetazolamide therapy was discontinued.

During the next four weeks the wound broke open intermittently and the eye became soft. Then, as the wound healed, tension would gradually rise. Finally, by the middle of August, the wound seemed firmly healed and tension rose to 50 mm. Gonioscopy revealed that the angle was largely closed by peripheral anterior synechias. Cyclodiathermy was done. After two weeks the eye became white and quiet and has remained so. The patient was last examined in November, 1957. Tension has been maintained in the low 20's with use of 4% pilocarpine four times a day. There are a clear pupillary opening, a few vitreous opacities, and probably no cupping of the disc. There are no cells or flare and no gross fundus pathology. Corrected vision equals counting fingers at 5 ft. The macula has evidently lost its function. Since July, 1956, the left eye has remained white and quiet and tension, 25 mm. or less with use of 4% pilocarpine four times a day. Vision gradually failed, and an intracapsular cataract extraction was done on this eye in November, 1957.

*Comment.*—The glaucoma in the left eye may have been primary open-angle glaucoma. There was never any definite evidence of secondary glaucoma. At any rate, it has been easily controlled with miotics.

The right eye has been for some time white and quiet and symptom-free, with tension well controlled, but vision is very low and does not improve.

This case illustrates the favorable response of lens-induced uveitis to removal of residual lens matter seven months after cataract extraction, too late to preserve good function in the eye.

CASE 10.—Extracapsular extraction followed by prolonged uveitis and glaucoma. The uveitis quickly subsided and tension remained under control after removal of residual lens cortex four months after cataract extraction. Persistent corneal edema and possible retinal detachment. Vision is hand movements.

A man, aged 68, was seen on Aug. 29, 1956. There was a history of detached retina in the right eye in 1946. Operation was

unsuccessful, and the eye became blind. There was a history of cataract extraction on the left eye on May 10, 1956. The eye has been continuously inflamed since the operation, and vision is very poor.

Examination. There was no light perception in the right eye. Tension was 71 mm. In the left eye vision equaled hand movements, with accurate light projection. Tension was 29 mm. There was marked congestion; the cornea showed epithelial edema throughout. The pupil was somewhat drawn up. There were capsular remains, with evidently some trapped cortex all around the pupillary border. There were many keratic precipitates in the lower cornea; 2% hydrocortisone drops was prescribed.

On Sept. 6, 1956, the eye was still markedly congested. Tension was 37 mm. The patient was admitted to the hospital and given acetazolamide and prednisone systemically and scopolamine and hydrocortisone locally.

On Sept. 12, 1956, the eye had whitened somewhat. Tension was 29 mm. An operation was done. A limbal incision was made above. The iris pillars and membrane were freed from the cornea with a spatula. The membrane was separated from the posterior surface of the iris with a spatula. The temporal pillar of the iris was excised. The membrane and cortical material were removed with forceps and by irrigation of the anterior chamber.

By Oct. 10, 1956, the eye was white and quiet, and it has remained so. Tension, with use of 250 mg. of acetazolamide twice a day and 4% pilocarpine four times a day, has been maintained at 22 mm. or less. The corneal edema has persisted unchanged, and vision has not improved beyond hand movements. There has been no recurrence of keratic precipitates on the cornea. In April, 1957, the eye became soft and subjectively the vision was worse. It was thought that the retina was probably detached, but because of the corneal edema the fundus could not be seen clearly.

*Comment.*—The dramatic quieting of the inflammation following removal of the lens remnants indicates that retained cortex was the cause of the inflammation. No useful vision was obtained, since the cornea never cleared and there may be a retinal detachment. Had the lens remnants been removed earlier, some vision might have been preserved.

Case 11.—Extracapsular cataract extraction followed by prolonged uveitis and glaucoma. Considerable temporary improvement following intravenous typhoid therapy. Discission three and again four months after operation. Complete subsidence of the inflammation 18 months after the cataract extraction. Dense pupillary membrane, hypotony, completely faulty light projection, presumed retinal detachment.

A man, aged 56, was first seen April 5, 1955, with a history of cataract extraction on the right eye two months previously. Since then the eye had been continuously inflamed and painful.

Examination. The left eye was white and quiet, with clear aphakic pupil; media were clear; fundus was normal. Tension was 17 mm. Corrected vision was 6/6.

The right eye was markedly congested; cornea, slightly hazy. The anterior chamber was normal in depth. There was a coloboma of the iris upward; the pupil was filled with a membrane in which there appeared to be some lens cortex. The iris vessels were dilated. There were many cells in the aqueous; tension was 27 mm.; vision equaled hand movements. Gonioscopically the angle was open except for anterior synechias at the tip of the iris pillars.

The patient was admitted to the hospital and given intravenous typhoid therapy, with marked improvement. In one week the eye became almost white.

The patient was next seen on Oct. 24, 1955. A needling had been done in May, 1955, and again in June. After the needling there was said to be considerable cortex in the anterior chamber. Since that time the condition of the eye had alternately improved and worsened. Sometimes the eye was almost white; at other times it became

much inflamed. Precipitates had been present on the cornea most of the time. Treatment had consisted of local application of steroids and scopolamine. Acetazolamide had been used periodically.

When examined on Oct. 24, 1955, the eye was mildly congested and the cornea was slightly hazy. There was a clear zone in the lower central part of the pupillary space with some vitreous herniating into the anterior chamber. The rest of the pupil and coloboma was filled with a membrane. There were many keratic precipitates on the cornea. There was a red reflex with the ophthalmoscope; the fundus was not seen. There were many vitreous opacities. Vision equaled hand movements. Tension was 30 mm. Gonioscopy showed the angle to be completely open except for anterior synechias of both pillars. Continued conservative treatment was advised.

The patient was next seen on Nov. 29, 1956. He stated that the eye had remained inflamed for several months after the last visit but that it had been quiet for two or three months. Examination revealed a white and quiet eye. The anterior chamber was of normal depth. The pupil was slightly drawn up, completely filled with a dense white membrane. There were almost complete posterior synechias. There were scars of old keratic precipitates on the cornea; there were no cells or flare. Tension was 6 mm.; light projection was faulty except temporally.

It was believed that there was undoubtedly detachment of the retina; the eye was essentially blind, and no further treatment was recommended.

*Comment.*—This case illustrates prolonged uveitis from retained cortex. The inflammation was temporarily lessened by intravenous typhoid and local and systemic steroid therapy. When the inflammation finally subsided the eye was blind, probably as a result of retinal detachment. In retrospect it seems altogether probable that if the residual lens cortex had been removed early in the course of the disease the eye could have been saved.

CASE 12.—Continuous severe inflammation for one and one-half years after extracapsular extraction. Enucleation. Pathologic report of lens-induced uveitis.

A man, aged 52, was first seen April 27, 1954. There was a history of bilateral cataract extraction one and one-half years previously. The right eye had been continuously inflamed ever since the operation; vision had been very poor, and there had been a great deal of pain in the eye.

The left eye was white and quiet. There were a coloboma of the iris upward and a clear aphakic pupil. The fundus was normal. Vision with correction was 6/6. Tension was 23 mm.

The right eye was markedly congested. There was an old prolapse of the temporal pillar at 1 o'clock, with possibly some filtration here. There were many keratic precipitates on the lower cornea. The iris vessels were markedly dilated, and there were new vessels on the iris. There was a membrane throughout the pupil and coloboma, in some areas thin enough to allow a faint red reflex. There was superficial vascularization of the cornea for 2 mm. all around the periphery. Vision was counting fingers at 5 ft. Tension was 20 mm. The eye was enucleated. The pathologic report was as follows.

*Gross Findings.*—The globe measured 25 mm. vertically, 24 mm. horizontally, and 24 mm. anteroposteriorly. There was a short stump of optic nerve, measuring 2 mm., attached. The cornea was opaque. At the superior temporal limbus there was a bleb of tissue containing pigment. The eye was opened horizontally. The vitreous was semifluid and almost totally opaque, with a white creamy appearance. No lens was seen. Upon removal of the inferior calotte a few strands of vitreous extending from the ora serrata to the nerve head were seen. The cut was made opposite to the suture.

*Microscopic Findings.*—The corneal epithelium was not remarkable. Small blood vessels extended through the midstroma al-

most to the center of the cornea. There was strand infiltration by polymorphonuclear cells but no abscess. Descemet's membrane was not clearly defined. A few mononuclear keratic precipitates were present on the endothelium. The iris was adherent to the cornea at the site of previous cataract section on the temporal side. The cornea seemed well healed here. On the nasal side, however, the iris was prolapsed into the site of the section, lining the cornea to form a staphyloma. At its thinnest point it seemed overlain only by conjunctiva. The conjunctiva here at the limbus showed pigment fragments, chronic inflammation cells, and occasional giant cells. The anterior chamber was relatively free of cells with the exception of a few macrophages, some of which covered the angle. The angle was open nasally but covered by the iris temporally. The iris was heavily infiltrated with plasma cells and macrophages. The ciliary processes had numerous macrophages on their surface, and a membrane extended between the ciliary processes on either side of the section. Its major component was lens capsule; lens material was present in small amounts among the capsule remnants. There were patches of chronic inflammatory cells, fibrous tissue, some acini, and pigment and plasma cells.

There were a few macrophages with eosinophilic cytoplasm in the vitreous. The choroid was not remarkable. The outer molecular layer of the retina was edematous and was forming a cyst in the macula. There was a new membrane forming over the retina, composed of hyaloid and macrophages. The disc was not cupped. The optic nerve was not remarkable.

*Diagnosis.*—Chronic endophthalmitis, probably secondary to lens reaction. No evidence of sympathetic disease.

*Comment.*—In view of the pathologic report and considering some of the other cases reported, it seems probable that if the retained lens matter had been removed, even one and one-half years after cataract extraction, the eye might have been saved. Because of the macular lesion, central acuity would probably not have been good, but useful peripheral vision might have been preserved.

### General Comment

Cases have been presented illustrating the severe uveitis and glaucoma which may be induced by free lens substance within the eye. The cases reported here, as well as those reported by Irvine and Irvine,[6] Courtney,[5] Leigh,[8] and MacDonald,[7] demonstrate the dramatic cure effected by prompt removal of the lens when an eye with hypermature cataract develops uveitis and glaucoma. The same is true if the lens is completely dislocated into the vitreous. Furthermore, it appears that uveitis and glaucoma due to the lens may occur even in cases of advanced immature cataract and may be relieved by removal of the lens.

How is the clinical diagnosis made? In an eye with an advanced hypermature cataract there is usually a rapid onset of redness and pain, with elevated tension. The tension may rise gradually and remain for a time only moderately elevated, or it may rise acutely and reach very high levels. One may observe only a mild flare in the anterior chamber, with a few cells, or the aqueous may be loaded with cells and there may be larger clumps of exudate or lens matter. The anterior chamber may be filled with crystals. In one of the cases here reported the anterior chamber was ultimately almost completely filled with purulent exudate. Heavy mutton-fat keratic precipitates may be observed. In cases where the lens is dislocated, elevated tension not controlled by the usual medical measures is the most prominent feature. In most of these cases there is a moderate number of cells in the aqueous. In one case here reported, lens matter ultimately appeared in the bottom of the anterior chamber. In other cases collections of exudate like keratic precipitates have been observed with the slit lamp on vitreous strands.

The cause of the glaucoma in these cases is presumed to be blockage of the trabecu-

lar meshwork by debris from the lens or by cells. Irvine and Irvine[6] have described macrophages on the surface of the meshwork and filling the trabecular spaces. Many eye pathologists have observed this picture in the angle, in similar cases. When gonioscopy is possible the angle is always found to be open. Grant[20] reported a markedly diminished outflow as measured by tonography in a case of hypermature cataract with acute glaucoma, with complete relief of the glaucoma and return to a normal facility of outflow after lens extraction. Evidently the washing out of the anterior chamber incident to lens extraction removes the lens debris and cells from the angle, which then regains its normal function, since the inflammation responsible for the cellular exudates ceases on removal of the lens.

Many eyes with hypermature cataract, uveitis, and glaucoma have been enucleated, since the glaucoma was not controlled by medical means and because the light projection was faulty. Faulty light projection in these cases is not unusual and is no contraindication to removal of the lens, since in most cases there is return of good function postoperatively and nothing abnormal is found in the fundus. In many reported cases the violent reaction in the affected eye had been preceded for months or years by cataract extraction on the fellow eye. The diagnosis in the affected eye has therefore sometimes been thought to be sympathetic uveitis, but the fellow eye in all cases has remained white and quiet, a situation never seen in true sympathetic ophthalmia. In all reported cases of hypermature cataract with uveitis and glaucoma in which the lens was not removed, eventually all vision was lost, and in most cases the eye was enucleated.

Pathologic examination of eyes with hypermature cataract removed for uveitis and glaucoma reveals a normal or near-normal posterior segment and suggests that these eyes could probably have been saved by a timely lens extraction.

Prompt removal of a traumatic cataract when uveitis with heavy mutton-fat keratic precipitates develops usually results in prompt subsidence of the inflammation, as in one of the cases reported here. Similar cases in which failure to remove the lens resulted in intractable uveitis and glaucoma with ultimate enucleation have been reported by Verhoeff and Lemoine[1] and Irvine and Irvine.[6]

After extracapsular extraction where there is residual lens cortex, in some cases there may be minimal postoperative reaction, eventually all the lens cortex is absorbed, and there is a good functional result. In these persons there is evidently no sensitivity to lens protein.

In other cases the postoperative course is somewhat stormy, indicating a mild degree of lens protein sensitivity, but the eye may quiet down in a few weeks with the usual conservative treatment. It is the cases which show very severe and prolonged postoperative inflammation which should cause the greatest concern. In these cases there is usually considerable residual cortex and probably a greater degree of sensitivity to lens protein.

The characteristic signs are marked congestion, cells in the aqueous, keratic precipitates on the cornea, and an elevated tension. The inflammatory process may be favorably influenced by mydriatics, local and systemic steroid therapy, and intravenous administration of typhoid vaccine, but it never entirely ceases until all residual lens matter is absorbed or removed. That conservative treatment may sometimes be successful is illustrated in one of the cases reported here, where, after a prolonged inflammation, the eye became quiet and regained good function. However, this case must be regarded as exceptional, and such conservative treatment is not advisable save for the milder cases in which there is very little residual cortex.

As is well illustrated in several of the cases reported here, delay in removal of residual lens cortex usually results in seri-

ous consequences to the eye. Prolonged lens-induced uveitis may lead to dense inflammatory pupillary membranes, inflammatory membranes extending backward to the retina and causing detachment, glaucoma from blockage of the angle meshwork by cells or debris or by peripheral anterior synechias, loss of macular function, and persistent corneal edema.

If operation to remove residual lens cortex is done within a few weeks after the lens extraction, the lens matter is usually easily removed by irrigation of the anterior chamber. If operation is delayed for several months, some of the lens matter is usually trapped in an inflammatory membrane and a more formidable operation is necessary. Adhesions between iris and membrane and iris and cornea must be freed; usually one or both iris pillars are excised and the capsular and cortical remains are removed with forceps and by irrigation of the anterior chamber. Vitreous loss has not occurred in any of the cases in which this operation has been done. The hyaloid membrane is invariably thickened, and sometimes there is an inflammatory membrane on its surface.

Removal of residual lens matter at any time, even several months after extracapsular extraction, has invariably resulted in a white and quiet eye. Residual glaucoma from peripheral anterior synechias may be a problem. In none of the cases in which removal of residual lens matter has been delayed for several months, though the eye became white and quiet, has the eye regained normal function.

Though conservative treatment in cases of lens-induced uveitis after extracapsular cataract extraction may occasionally be successful in quieting the inflammation and preserving useful function, early removal of residual lens cortex in such cases is to be recommended as the treatment of choice. It is effective at any time after the cataract extraction in quieting the inflammation, but useful function of the eye is generally lost if there is a delay in removal of residual lens cortex.

## Summary and Conclusions

The literature dealing with lens-induced uveitis and glaucoma is reviewed and case reports are presented to illustrate these complications. Free lens substance in the eye may give rise to little or no inflammatory reaction. On the other hand, it may give rise to severe reaction which is amenable to timely removal of the lens or residual lens matter. Such cases include those with hypermature cataracts, whether in situ or dislocated into the vitreous; advanced immature cataracts; traumatic cataracts, and those following extracapsular cataract extraction. If the lens substance is not removed in these cases with lens-induced inflammation, the eye will usually be lost or seriously damaged.

Verhoeff's dictum [19] that it is better to remove the offending lens or residual lens matter than to remove the eye is amply confirmed by clinical observation.

5 Bay State Road (15).

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# A New Syndrome

*Dyscephalia with Bird Face and Dental Anomalies, Nanism, Hypotrichosis, Cutaneous Atrophy, Microphthalmia, and Congenital Cataract*

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## Introduction

The literature comprises 21 reports on cases showing very similar symptom complexes, sufficiently identical to be regarded as a well-defined clinical entity and as a new, autonomous syndrome to be linked into the long chain of heredity of ectodermal dysplasia.

The cases which I culled from the literature were described under the following variety of names: sutural congenital alopecia (Aubry, 1893); congenital cataract with cranial anomaly (Bergmeister, 1911); progeria complicated by microphthalmia (Schondel, 1943); progeria with nanism and congenital cataract (Moehlig, 1946); bird face and congenital cataract (Hallermann, 1948); mandibulofacial malformation and ocular changes (Streiff, 1950; Nizetic, 1954); Vogt-Koyanagi-like syndrome with mandibulofacial dysostosis (Ludwig and Korting, 1950); dyscephalia with congenital cataract and hypotrichosis (Ullrich and Fremerey-Dohna, 1953; Weyers, 1954; Leffertstra, 1956); congenital ectodermal dysplasia (Gregory, 1955); progeria with ocular anomalies (Gregersen, 1956); mandibulofacial dysostosis (Blodi, 1957).

### Positive Signs

As I analyzed these cases I found that they invariably showed the same essential signs. These are the following seven:

(1) *Dyscephalia and Bird Face.*—Scaphocephaly or brachycephaly; mandibular aplasia; thin, pointed nose—features combining to form a countenance which lends all subjects affected a "familiar face."

(2) *Dental Anomalies.*—Teeth missing, badly implanted, and deformed; open bite.

(3) *Proportionate Nanism*

(4) *Hypotrichosis.*—This is particularly marked on hairy parts of the skin (alopecia areata) and in the eyelashes and eyebrows.

(5) *Atrophy of the Skin.*—This is as a rule localized to the head and particularly to the nose.

(6) *Bilateral Microphthalmia*

(7) *Congenital Cataract.*—This is bilateral, and it may be total or incomplete.

### Negative Signs

In addition, mention should be made of certain negative signs which are of importance in differentiating this syndrome from other more or less related conditions, as follows:

1. There are no anomalies of the ear such as are a constant finding in syndromes originating from the first arch, viz., otomandibular dysostosis (François and Haustrate, 1954) and mandibulofacial dysostosis (Franceschetti and Klein, 1949).

2. There are no palpebral anomalies such as are also a constant phenomenon in mandibulofacial dysostosis (Franceschetti and Klein, 1949).

3. There is no muscular atrophy, chronic arthritis with deformity of the joints, or premature arteriosclerosis, as seen in progeria.

4. There are no anomalies of the nails, as in certain ectodermal dysplasias, nor anomalies of the extremities, as in certain types of dyscephalia.

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Figure 1

5. There is no or only slight mental backwardness; both neurological and psychological findings are as a rule negative.

**Observations from the Literature**

The following are summaries of the observations culled from the literature.

CASE 1 (Aubry, 1893; Fig. 1).—A youth aged 16 years showed the following symptoms:

(1) *Dyscephalia.*—Dented skull with occipital protrusion and prominent frontal humps; mandibular aplasia.

(2) *Dental Anomalies.*—Irregular implantation of teeth.

(3) *Nanism.*—No information on height or stature.

(4) *Hypotrichosis.*—There was "sutural congenital alopecia"; the skin over the cranial sutures was hairless, and there was a small patch behind each ear where the hair was thinning.

(5) *Atrophy of the Skin.*—The skin over the cranial sutures was dry, thin, pale, taut, and sclerous.

(6) *Microphthalmia.*—No information on the size of the eyeballs.

(7) *Cataract.*—Mention is made of bilateral congenital cataract, with blindness.

CASE 2 (Bergmeister, 1911; Fig. 2).—A girl aged 12 years showed the following symptoms:

(1) *Dyscephalia.*—Marked curvature of the parietal bones and the occipital bone, dehiscence of the lambdoid and the longitudinal suture, open fontanelles, bird face, thin curved nose (parrot beak), and marked hypoplasia of the mandible.

(2) *Dental Anomalies.*—Absence of the third molar.

(3) *Nanism.*—Body height 123 cm. instead of 144 cm.

(4) *Hypotrichosis.*—"Sutural" alopecia, with thin eyebrows and short, fine eyelashes.

(5) *Skin.*—No information on the state of the skin.

(6) *Bilateral Microphthalmia.*—The diameter of the cornea was 9 mm.

(7) *Cataract.*—Total congenital cataract with nystagmus.

CASE 3 (Schondel, 1943; Fig. 3).—A girl aged 12 years showed the following symptoms:

(1) *Dyscephalia.*—Square cranium of hydrocephalic appearance, relatively overdeveloped as compared with the face; prominence of frontal tuberosities; narrow curved nose; marked aplasia of the mandible.

(2) *Dental Anomalies.*—Faulty implantation and caries of teeth.

(3) *Nanism.*—Body height 120 cm. instead of 144 cm.; body weight 20.5 kg. instead of 35 kg.

Figure 2

Figure 3

(4) *Hypotrichosis.*—Scanty growth of thin, whitish hairs; lack of eyelashes and eyebrows.

(5) *Atrophy of the Skin.*—The skin of the head was atrophic, taut, and heavily veined.

(6) *Bilateral Microphthalmia.*—The diameters of the cornea were each 8 mm.

(7) *Cataract.*—There was no cataract, but there were sequelae of uveitis, viz., old precipitates on the Descemet membrane, posterior synechiae, and organized pupillary exudates. There were intermittent convergent strabismus and horizontal and rotatory nystagmus.

*Other Signs.*—Other particulars mentioned were scantiness of subcutaneous adipose tissue, underdeveloped muscles, lordosis, and "winged" shoulder blades.

CASE 4 (Schondel, 1943; Figs. 4 and 5).—A boy aged 8 years showed the following symptoms:

(1) *Dyscephalia.*—Enlarged cranium, overdeveloped as compared with the facial skull and suggestive of hydrocephaly; prominent frontal tuberosities; fine, narrow, pointed curved nose (beak type); manifest mandibular aplasia; ogival palate.

(2) *Dental Anomalies.*—Irregular implantation and caries of teeth.

(3) *Nanism.*—Body height 102 cm. instead of 124 cm.; body weight 15.3 kg. instead of 24.5 kg.

(4) *Hypotrichosis.*—Scanty hair growth and localized baldness; eyebrows virtually lacking, with scanty and short eyelashes.

(5) *Atrophy of the Skin.*—The cranial skin, and particularly that of the nose, was delicate, atrophic, taut, and heavily veined.

(6) *Bilateral Microphthalmia.*—Present, with a corneal diameter of 7 mm.

Figure 4

(7) *Cataract.*—Bilateral congenital cataract with convergent strabismus and nystagmus.

*Other Signs.*—Mention is also made of blue sclerae, lordosis, spina bifida, and "winged" shoulder blades.

CASE 5 (Moehlig, 1946; Fig. 6).—A boy aged 5 years showed the following symptoms:

Figure 6

(4) *Hypotrichosis.*—Scanty hair growth; bald frontal region; hardly any eyebrows, and no eyelashes.

(5) *Atrophy of the Skin.*—Cranial and facial skin surfaces dry, delicate, and taut.

(6) *Microphthalmia.*—No information on the size of the eyeballs and the corneae.

(7) *Cataract.*—Bilateral congenital cataract, incomplete, with divergent strabismus and pendular nystagmus.

*Other Signs.*—Blue sclerae; osteoporosis, especially marked in the phalanges and

Figure 5

(1) *Dyscephalia.*—Microcephaly, with a cranial circumference of 47 cm. instead of 52 cm.; dehiscence of the sagittal and the lambdoid suture; narrow aquiline nose; aplasia of the mandible; small mouth; ogival palate, and bird face.

(2) *Dental Anomalies.*—Badly implanted, small, carious teeth.

(3) *Nanism.*—Body height 96.5 cm. instead of 108 cm.; body weight 12 kg. instead of 18.5 kg.

Figure 7

Figure 8

metacarpal bones, and some mental backwardness.

Case 6 (Haliermann, 1948; Fig. 7).—A man aged 25 years showed the following symptoms:

(1) *Dyscephalia.* — Brachycephaly with mandibular aplasia; thin parrot-beak nose; bird face.

(2) *Dental Anomalies.*—Present.

(3) *Nanism.*—Present.

(4) *Hypotrichosis.*—Scanty hair growth and eyebrows.

(5) *Atrophy of the Skin.*—Atrophy of the skin of the nose.

(6) *Bilateral Microphthalmia.*—Corneal diameter not exceeding 10 mm.

(7) *Cataract.*—Bilateral congenital cataract with peripapillary choroid atrophy.

Case 7 (Hallermann, 1948; Fig. 8).—A man aged 55 years showed the following symptoms:

(1) *Dyscephalia.*—Brachycephaly; bird face, with mandibular aplasia, thin nose, and receding chin.

(2) *Dental Anomalies.* — Malformation of teeth.

(3) *Nanism.*—No information on body height.

(4) *Hypotrichosis.* — Hypotrichosis, especially of the eyebrows.

(5) *Atrophy of the Skin.*—Atrophy of the skin, particularly of the nose; numerous folds in the facial skin; double chin.

(6) *Bilateral Microphthalmia.*—The corneal diameter was 11 mm. on the right and 10 mm. on the left.

(7) *Cataract.*—Bilateral congenital cataract associated with peripapillary choroid atrophy tapering to the temporal region, horizontal nystagmus with a rotatory component when the patient was looking to the

Figure 9

Figure 10

left, and concomitant divergent strabismus of the left eye.

CASE 8 (Marchesani, 1949; Fig. 9).—A male of unspecified age showed the following symptoms:

(1) *Dyscephalia.*—Brachycephaly with prominent frontal bosses; mandibular aplasia, bird face.

(2) *Dental Anomalies.*—Malposition of teeth.

(3) *Nanism.*—No information on body height.

(4) *Hypotrichosis.*—Cranial hypotrichosis; bald patches especially in the frontal regions.

(5) *Skin.*—The condition of the skin is not described.

(6) *Bilateral Microphthalmia.*—Present.

(7) *Bilateral Congenital Cataract.*—Present.

CASE 9. (Marchesani, 1949; Fig. 10).—A male of unspecified age showed the following symptoms:

(1) *Dyscephalia.*—Brachycephaly, mandibular aplasia, bird face.

(2) *Dental Anomalies.*—Malposition of teeth.

(3) *Nanism.*—No information on body height.

(4) *Hypotrichosis.*—No information on hair growth.

(5) *Skin.*—No information on the skin.

(6) *Bilateral Microphthalmia.*—Present.

(7) *Bilateral Congenital Cataract.*—Present.

CASE 10 (Streiff, 1950; Fig. 11).—A woman aged 31 years showed the following symptoms:

(1) *Dyscephalia.*—Microcephaly, with a narrow elevated frontal region; the nose thin, long, and pointed, reminiscent of a parrot beak; mandibular hypoplasia with receding chin; ogival palate; bird face.

(2) *Dental Anomalies.*—Anomalous implantation of teeth.

(3) *Proportionate Nanism.*—The height was only 140 cm.

(4) *Hypotrichosis.*—Marked hypotrichosis of the hairy parts of the skin; eyebrows were almost completely lacking, and eyelashes were partly lacking.

Figure 11

Figure 12

(5) *Skin.*—Atrophy of the skin, particularly marked on the nose; the chin seemed to be divided by a central cleft; double cutaneous chin.

(6) *Bilateral Microphthalmia.*—Present, with a corneal diameter of 8 mm.

(7) *Cataract.*—Total congenital cataract, with foci of chorioretinal atrophy.

CASE 11 (Ludwig and Korting, 1950; Fig. 12).—A boy aged 15 years showed the following symptoms:

(1) *Dyscephalia.*—Prominence of the parietal bones and the occipital bone, narrow frontal bone, dehiscence of the lambdoid and the sagittal suture, flattened occiput, more-or-less-triangular cranial vault, receding forehead, aplasia of the malar bone, thin nose, marked mandibular hypoplasia, ogival palate.

(2) *Dental Anomalies.*—Unsatisfactory implantation of teeth; open bite.

(3) *Nanism.*—No information on body height.

(4) *Hypotrichosis.*—The hairy parts of the skin showed polycyclic plaques in which hair was thin, scanty, and silvery; the periphery of the hairy parts showed round, circumscribed bald patches; lateral parts and eyebrows and eyelashes were scanty.

(5) *Atrophy of the Skin.*—This was especially marked on the nose; there were sharply circumscribed depigmentations on the trunk (vitiligo).

(6) *Bilateral Microphthalmia.*—Present.

(7) *Cataract.*—Bilateral incomplete congenital cataract.

*Other Signs.*—Other ocular changes included an anti-Mongoloid inclination of the palpebral fissures, an indentation in the external one-third of the lower palpebral margin, slight ptosis, blue sclerae, atrophy of the iris, an amorphous retrocrystalline membrane, convergent strabismus, and pendular nystagmus. Further general changes included lordosis and scoliosis, cryptorchism, and hypogenitalism.

CASE 12 (Ullrich and Fremerey-Dohna, 1953; Fig. 13).—A girl aged 27 months showed the following symptoms:

(1) *Dyscephalia.*—Brachycephaly; flattened trapezoid cranial vault; flattened occipital region; prominent frontal bosses; marked parietal arching; dehiscence of cranial sutures; open fontanelles; unmistakable mandibular hypoplasia, less marked maxillary hypoplasia; receding chin; small, thin nose; vaulted palate.

(2) *Dental Anomalies.*—No mention of dental anomalies.

(3) *Nanism.*—Body height is not given, but authors mention "slender physique."

(4) *Hypotrichosis.*—A certain hypotrichosis. Hair growth scanty in the center and in the frontal part of the cranium.

(5) *Atrophy of the Skin.*—This was particularly marked on the nose, where the skin was excessively thin and showed fine venous ectasias.

(6) *Bilateral Microphthalmia.*—Present, with a corneal diameter of 9.5 mm. on the right and 9 mm. on the left.

(7) *Bilateral Congenital Cataract.*—Complete, with internal concomitant strabismus, pendular nystagmus, dissociated move-

Figure 13

Figure 14

ments of the eyeballs, and posterior synechiae.

*Other Signs.*—Mention is also made of an anti-Mongoloid inclination of the palpebral fissures.

CASE 13 (Weyers, 1954; Figs. 14 and 15).—A boy aged 16 years showed the following symptoms:

(1) *Dyscephalia.*—A trapezoid cranium with an increase in the biparietal diameter and occipital flattening; hypoplasia of the temporal wall of the orbits; hypoplasia of the nasal bone, which was thin and curved inward; aplasia of the mandible.

(2) *Dental Anomalies.*—Hiatodontia.

(3) *Nanism.*—There was no nanism, body height being 170 cm.

(4) *Hypotrichosis.*—Bald patches in the hairy parts of the skin (alopecia areata), particularly in the region of the larger sutures (sutural alopecia); the right eyebrow scanty on the nasal side: the left eyebrow lacking; scanty eyelashes.

(5) *Atrophy of the Skin.*—This was marked in the cranial and facial region; the skin was thin, leukodermal, and heavily veined.

(6) *Bilateral Microphthalmia.*—Present, with a corneal diameter of 8 mm.

(7) *Eye Findings.*—Aphakia on the right and inferonasal crystalline opacities on the left, with bilateral amblyopia and a floating vitreous body, divergent strabismus, nystagmus, and blue sclerae.

CASE 14 (Nizetic, 1954; Fig. 16).—A boy aged 11 years showed the following symptoms:

(1) *Dyscephalia.*—Platybasia and slight sutural diastasis, thinning of the cranial roof, partial calcification of the cerebellar roof, marked digital impressions, perisellar hyperostosis, interclinoid bridge, marked mandibular hypoplasia, vaulted palate, facial asymmetry with underdevelopment on the right, parrot face.

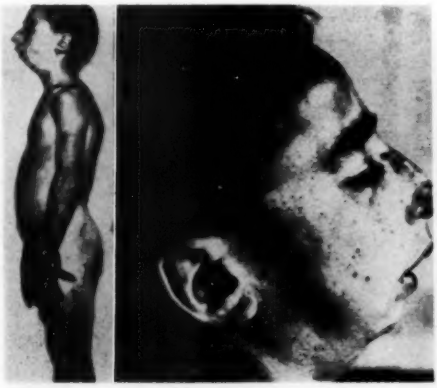

Figure 16

(2) *Dental Anomalies.* — Malformation and caries of teeth.

(3) *Nanism.*—Body height 113 cm. instead of 137 cm.; somatic and skeletal development markedly retarded.

(4) *Hypotrichosis.*—There seemed to be no hypotrichosis.

(5) *Cutaneous Atrophy.*—This was particularly marked on the nose.

(6) *Microphthalmia.*—There was no mention of microphthalmia, which was, however, likely to exist in view of very

Figure 15

marked hypermetropia (18 D.) even if aphakia is taken into account.

(7) *Cataract.*—There was total bilateral congenital cataract, for which operation had been done at the age of 4 (one side) and at the age of 5 (contralateral side).

*Other Signs.*—Mention is also made of slight divergent strabismus on the left, blue sclerae, and cherry-red macula surrounded by a slightly raised grayish zone.

There were also signs of status dysraphicus: slight scoliosis, barrel chest, marked hypotrophy of the musculature of the scapular region with "winged" shoulder blades, spina bifida, platyspondylia, diffuse osteoporosis; claw hands, marked hypogenitalism, and slight mental retardation.

Figure 17

CASE 15 (Gregory, 1955; Fig. 17).—A girl aged 7 years showed the following symptoms:

(1) *Dyscephalia.* — Open fontanelles, mandibular aplasia.

(2) *Dental Anomalies.*—Malformation of teeth.

(3) *Nanism.*—Body height 116 cm. instead of 118 cm.

(4) *Hypotrichosis.*—Scanty light-colored hair; no eyebrows.

Figure 18

(5) *Atrophy of the Skin.*—There was atrophy of the skin, which was soft and dry.

(6) *Microphthalmia.*—There was no information on the size of the eyeballs.

(7) *Bilateral Congenital Cataract.*—Present, operated on by discission.

CASE 16 (Gregory, 1955; Fig. 18).—A girl aged 10 years showed the following symptoms:

(1) *Dyscephalia.* — Marked mandibular hypoplasia.

(2) *Dental Anomalies.*—No information on the teeth.

(3) *Nanism.*—Body height 120 cm. instead of 132 cm.

(4) *Hypotrichosis.*—Scanty growth of light-colored hair; a patch of alopecia at the level of the vertex.

(5) *Atrophy of the Skin.*—The skin was dry and somewhat rough.

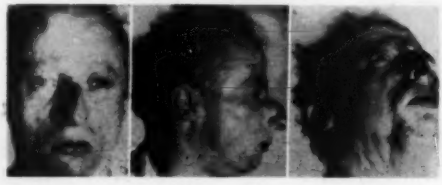

Figure 19

Figure 20

(6) *Microphthalmia.*—There was no information on the size of the eyeballs.

(7) *Bilateral Congenital Cataract.*—Present, treated by discission.

*Other Signs.*—Other changes mentioned are syndactylism and coxalgia.

Case 17 (Leffertstra, 1956; Fig. 19).—A man aged 31 years showed the following symptoms:

(1) *Dyscephalia.* — Brachycephaly with raised frontal aspect and prominent frontal bosses; thin, long parrot-beak nose; hypoplasia of the mandible with receding chin; vaulted palate.

(2) *Dental Anomalies.*—Caries.

(3) *Proportionate Nanism.* — Present, body height 155 cm. and body weight 50 kg.

(4) *Hypotrichosis.*—Scanty hair growth on all cranial areas, particularly the forehead; axillary and pubic hair scanty.

(5) *Skin.*—No information on the condition of the skin.

(6) *Bilateral Microphthalmia.*—The corneal diameter did not exceed 10 mm.; there was hypermetropia (6 D.).

(7) *Cataract.*—There were soft bilateral congenital cataracts.

Case 18 (Gregersen, 1956; Fig. 20).—A man aged 22 years showed the following symptoms:

(1) *Dyscephalia.*—Prominent forehead, curved nose, mandibular hypoplasia, and bird face.

(2) *Dental Anomalies.*—No information on dental condition.

(3) *Nanism.*—Body height 138 cm.

(4) *Hypotrichosis.*—Scanty hair; frontal alopecia; short, pale eyelashes and eyebrows.

(5) *Atrophy of the Skin.*—Delicate atrophic skin, heavily veined.

(6) *Bilateral Microphthalmia.*—Present, with a corneal diameter of 8.5 mm.; very convex cornea.

(7) *Total Bilateral Congenital Cataract.*—Present.

*Other Signs.*—Other changes mentioned: pale discs, small disseminated pigmentations in the fundus of the right eye; nystagmus and convergent strabismus at the age of 8; this patient is the same as the one described by Schondel (1943, Case 4).

Case 19 (Gregersen, 1956; Fig. 21).—A woman aged 25 years showed the following symptoms:

Figure 21

(1) *Dyscephalia.*—Prominent forehead, mandibular hypoplasia, bird face, double chin.

(2) *Dental Anomalies.*—No information on dental condition.

(3) *Nanism.*—Present.

(4) *Hypotrichosis.*—Alopecia; eyelashes and eyebrows scanty.

(5) *Atrophy of the Skin.*—Delicate, atrophic skin.

(6) *Bilateral Microphthalmia.*—Present, with a corneal diameter of 7.0 mm.; very convex cornea.

(7) *Cataract.*—Although no cataract was observed at the age of 5 (?), a membranous conversion of both lenses was seen at the age of 15 (spontaneous absorption of the crystalline lens).

*Other Signs.*—Nystagmus, convergent strabismus, and ocular hypertension on the right.

CASE 20 (Blodi, 1957).—A woman aged 37 years showed the following symptoms:

(1) *Dyscephalia.*—Parrot-beak nose, aplasia of the mandible, bird face, and aged physiognomy.

(2) *Dental Anomalies.*—No information on dental condition.

(3) *Nanism.*—Present.*

(4) *Hypotrichosis.*—No eyebrows; scanty eyelashes.

(5) *Skin.*—No information on the condition of the skin.

(6) *Bilateral Microphthalmia.*—Present.

(7) *Bilateral Membranous Congenital Cataract.*—Present.

* Blodi, F. C.: Personal communication to the author.

Figure 22

Figure 23

*Other Signs.*—Distichiasis of the left upper eyelashes and an anti-Mongoloid inclination of the palpebral fissures.

CASE 21 (Blodi, 1957; Fig. 22).—A girl aged 8 years showed the following symptoms:

(1) *Dyscephalia.*—Bird face and aged physiognomy; malformation of a curved nose; mandibular aplasia; facial asymmetry due to right hemiatrophy.

(2) *Dental Anomalies.*—Malposition and absence of some teeth.

(3) *Nanism.*—Body height 112 cm. instead of 123 cm.; body weight 15.3 kg. instead of 24 kg.

(4) *Hypotrichosis.*—Marked cranial hypotrichosis; right eyebrow virtually lacking.

(5) *Atrophy of the Skin.*—Present, with marked venosity.

(6) *Bilateral Microphthalmia.*—Present.

(7) *Cataract.*—Complete right-sided congenital cataract and incomplete cataract on the left, with convergent strabismus in the right eye.

## Report of a Case

A personal observation can be added to the above reports from the literature.

CASE 22.—A boy, an only child aged 13 years 8 months when seen, showed an unusual craniofacial development, present since birth, and developmental retardation. No other similar cases existed in the family. There was no parental consanguinity.

The patient showed all the symptoms described in the above case reports.

(1) *Dyscephalia* (Figs. 23 and 24).—(*a*) Cranium: There was a certain degree of microbrachycephaly. X-rays (Professor De Witte) showed slight hyperostosis around the sutures, which were well visible. The base of the skull and the sella turcica were flattened. The flattening was oblique. There was considerable synchondrosis between the sphenoid and the occipital bone.

Figure 24

(*b*) Face: The face was small and deformed although symmetrical. The nasofrontal angle was sharper than normal. There was some hypoplasia of the maxilla with relative prognathism. On the other hand, there was true aplasia of the mandible with retrognathism; the mandibular body was not larger than 43 mm. (instead of 73 mm.); the ascending rami were markedly shortened, and the condyles were lacking.

Figure 25

These anomalies, together with a thin and slightly curved nose, combined to form a bird face.

(2) *Dental Anomalies* (Professor Comhaire Fig. 25).—There were an open bite and malocclusion of the lower molars. The following teeth were lacking: in the maxilla, the right canine, left lateral incisor, and second left premolar; in the mandible, the incisors. The mandible showed persistance of certain deciduous teeth, viz., the canines and molars. The lacking teeth were not subject to inclusion, with the exception of the second right upper premolar. The teeth found, although badly implanted, were not carious or only slightly so; their calcification corresponded with the age of 10 years 6 months.

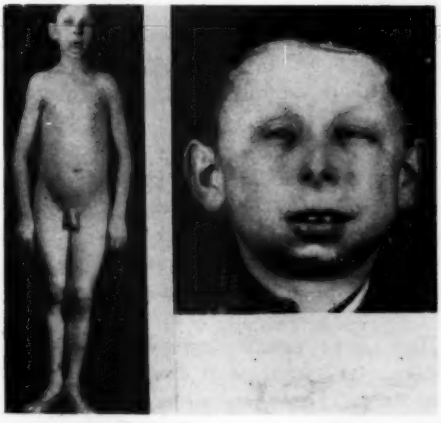

Figure 26

Figure 27

(3) *Nanism* (Fig. 26).—There was proportionate, harmonious nanism, the body height being 131 cm. instead of 152 cm., and the body weight, 27.2 kg. instead of 41.5 kg.

Skeletal development was retarded; the bone age was 10 to 11 years. The nucleus of the pisiform bone is normally seen at the age of 10; it was hardly visible in this case. At the age of 14 the trochlea of the humerus should be firmly formed; it was not.

At the age of 9 the trochiter merges with the humerus; in this case the growth line was still visible. At the age of 11 the nucleus of the lesser femoral trochanter is seen; in this case it was not yet visible.

Yet there was no skeletal malformation; the spinal column in particular was normal.

(4) *Hypotrichosis* (Fig. 27).—There was alopecia areata, particularly on the posterior cranial surface and at the temples; no club hairs were actually visible. There were a few patches of cicatricial alopecia, explained by the mother as a result of a pyoderma of the hairy scalp in the history. There were virtually no eyebrows. Eyelashes were scanty and completely lacking in places. There was no axillary or pubic hair growth.

(5) *Atrophy of the Skin.*—The skin was delicate, particularly on the head. It was particularly atrophic, thin, and discolored on the nose, where a network of veins was distinctly seen. Near the right upper border of this atrophic zone, on the bridge of the nose, there was a minute telangiectasis. The thighs, particularly the popliteal hollows, were livid. There was no anomalous pigmentation or other dermatological anomalies (Professor Pierard).

(6) *Bilateral Microphthalmia.*—The corneal diameter was 10 mm. on each side.

(7) *Cataract.*—There was total bilateral congenital cataract, for which patient underwent an operation (discission) at the age of 7 months.

*Other Ocular Changes.*—There was horizontal nystagmus, most marked in the lateral aspect. The right eye was more endophthalmic than the left and showed slight internal strabismus. Ophthalmoscopic examination showed a coloboma at the entrance of the optic nerve on the right, and on the left there were peripapillary changes, viz., a normal papilla surrounded by some small foci of cicatricial chorioretinitis; on the temporal side of the papilla there was a more marked focus, twice as large as the diameter of the disc and with an irregularly rounded ex-

ternal margin, highly pigmented and clearly circumscribed.

The intraocular tension and the refringent media were normal.

Vision did not exceed 1/40 on the right and 1/20 on the left after correction of the aphakia.

*Supplemental Examinations.*—(1) General Examination (Professor Hooft): Internal and neurological findings were entirely negative. There was merely a slight retardation in mental development.

The urine was normal. Hematological examination showed Hb. 105%; erythrocytes 4,060,000 per cubic millimeter; leucocytes 4400 per cubic millimeter; thrombocytes 180,000 per cubic millimeter; reticulocytes, 1 per 1000; differential count, eosinophils 5%, staff cells 1%, segmented neutrophils 33%, and lymphocytes 61%.

Erythrocyte sedimentation rate was 6/14; uremia, 0.3 gm/100 ml., and glycemia, 105 mg/100 ml.; calcium level was 10.8 mg/100 ml.; phosphorus, 4.5 mg/100 ml.; alkaline phosphatase, 6.1 units/100 ml.; sodium 320 mg/100 ml.; potassium, 18.5 mg/100 ml.; chlorides, 610 mg/100 ml. Total protein value was 8 gm/100 ml.; total lipid value, 705 mg/100 ml.; cholesterol, 226 mg/100 ml.; free cholesterol 39 mg/100 ml.; cholesterol esters, 187 mg/100 ml.; bilirubin, 1.3 mg/100 ml.; thymol turbidity, 8.7 units; zinc sulfate test, 17.9 units.

Electrophoretic determination of serum proteins gave the following results: albumin 51.5% = 4.12 gm/100 ml.; $\alpha_1$-globulins 3.9% = 0.31 gm/100 ml.; $\alpha_2$-globulins 7.5% = 0.60 gm/100 ml.; $\beta$-globulins 9.5% = 0.76 gm/100 ml.; $\gamma$-globulins 27.6% = 2.21 gm/100 ml.

Endocrine examination gave the following results: Thorn test with corticotropin (ACTH), positive; urinary 17-ketosteroid excretion, 0.3 mg/24 hours; 11-oxysteroids, 0.1 mg/24 hours.

Important among these findings are the increased $\gamma$-globulin level and the very low steroid excretion in the urine.

(2) Otorhinological Examination (Professor Eeman): There were no anomalies of the external ear or the auditory canal. The very oblique insertion of the tympanum was of the embryonic type. Audiometric results were normal. The nasal septum showed a deviation to the left.

(3) Electroencephalographic Examination: The spontaneous records showed regular activity, symmetrical and synchronized. The occipital rhythm had a frequency of 10 cps and an amplitude of 60$\mu$V. There were no slow waves, and no paroxysmal activity was seen.

Stroboscopic reactivation. An isolated stimulus gave a very constant specific occipital response: b wave onset, 55 milliseconds; culmination of b wave 95 milliseconds; culmination of c wave 115 milliseconds. At a frequency of 1 to 10 stimuli per second the cortex followed the rhythm; driving cortex (8 to 10 cps). At an increased frequency of 18 to 20 stimuli per second there was marked slowing in the rhythm, with increase in amplitudes in all leads: 4 to 5 cps and 200$\mu$V. At this moment the patient felt considerable anxiety.

## Symptomatology

The observations described show that the syndrome is characterized by seven chief symptoms.

(1) Dyscephalia, comprising dyscrania, on the one hand, and a mandibulofacial malformation, on the other.

(*a*) The dyscrania sometimes consists of scaphocephaly but more often of brachycephaly.

Scaphocephaly, with the cranium in the shape of the hull of a ship and with protruding forehead, has been observed by Aubry (1893); brachycephaly with platysbasia was seen by Hallermann (1948), Marchesani (1949), Ullrich and Fremerey-Dohna (1953), Nizetic (1954), Leffertstra (1956), and me. An occipital protrusion was seen by Bergmeister (1911) and Ludwig and Korting (1950), and frontal protrusion

(prominence of the frontal bosses), by Schondel (1943, Case 3), Marchesani (1949), Ullrich and Fremerey-Dohna (1953), Leffertstra (1956), and Gregersen (1956). Bulging of the parietal bones was mentioned by Bergmeister (1911), Schondel (1943, Case 4), Ludwig and Korting (1950), Ullrich and Fremerey-Dohna (1953), and Weyers (1954). In some cases the forehead was narrow, elevated, and receding (Streiff, 1950; Ludwig and Korting, 1950; Leffertstra, 1956). There may be aplasia of the malar bone (Ludwig and Korting, 1950; Weyers, 1954).

While there is sometimes microcephaly (Moehlig, 1946; Streiff, 1950, and personal observation), there may also be relative hydrocephaly (Schondel, 1943, Case 3).

The lambdoid and the longitudinal sutures are often dehiscent (Bergmeister, 1911; Moehlig, 1946; Ludwig and Korting, 1950; Ullrich and Fremerey-Dohna, 1953; Nizetic, 1954), and the fontanelles, open (Bergmeister, 1911; Ullrich and Fremerey-Dohna, 1953; Gregory, 1955, Case 15).

Nizetic (1954) mentioned thinning of the cranial bone, partial calcification of the cerebellar roof, marked digital impressions, perisellar hyperostosis, and an interclinoid bridge. In our patient there were hyperostosis around the cranial sutures and a wide synchondrosis between the sphenoid and the occipital bone.

(*b*) The mandibulofacial malformation is characterized above all by mandibular aplasia, which was unmistakable in all cases. The maxilla was sometimes also slightly hypoplastic (personal observation).

Mention has also been made of a thin, tapering, pointed nose (Bergmeister, 1911; Schondel, 1943, Cases 3 and 4; Moehlig, 1946; Hallermann, 1948, Cases 6 and 7; Streiff, 1950; Ludwig and Korting, 1950; Ullrich and Fremerey-Dohna, 1953; Weyers, 1954; Leffertstra, 1956; personal observation), accompanied by hypoplasia of the nasal bone (Weyers, 1954), which is often curved and shaped like a parrot beak (Bergmeister, 1911; Schondel, 1943, Case 3; Moehlig, 1946; Hallermann, 1948; Streiff, 1950; Leffertstra, 1956; Gregersen, 1956; Blodi, 1957, Cases 20 and 21; personal observation).

The nasofrontal angle is more acute than normal (personal observation).

The palate is as a rule vaulted (Schondel, 1943, Case 4; Moehlig, 1946; Streiff, 1950; Ludwig and Korting, 1950; Ullrich and Fremerey-Dohna, 1953; Nizetic, 1954; Leffertstra, 1956).

Nizetic (1954) and Blodi (1957, Case 21) mentioned facial asymmetry due to hemiatrophy.

Dyscephalia with aplasia of the mandible and thin, curved nose gives the patient a bird profile, more particularly a parrot profile. The frequent presence of a double cutaneous chin with a central cleft also contributes toward giving these patients a characteristic physiognomy (Hallermann, 1948, Case 7; Streiff, 1950; Gregersen, 1956, Case 19; Blodi, 1957, Case 21; personal observation).

(2) Dental anomalies are a virtually constant feature: Certain teeth may be lacking (Bergmeister, 1911; Blodi, 1957; personal observation). Those teeth which are present are often malformed (Moehlig, 1946; Hallermann, 1948, Cases 6 and 7; Nizetic, 1954; Gregory, 1955) or irregularly implanted (Aubry, 1893; Schondel, 1943, Cases 3 and 4; Moehlig, 1946; Marchesani, 1949; Streiff, 1950; Ludwig and Korting, 1950; Blodi, 1957; personal observation). Open bite is not uncommon (Ludwig and Korting, 1950; personal observation), nor is hiatodontia (Weyers, 1954). Caries are frequent and early (Schondel, 1943, Cases 3 and 4; Moehlig, 1946; Nizetic, 1954; Leffertstra, 1956).

(3) Harmonious, proportionate nanism was mentioned in 15 cases of 22, body height being 13 to 24 cm. below the normal (Aubry, 1893; Hallermann, 1948, Case 7; Marchesani 1949, Cases 8 and 9; Ludwig and Korting, 1950; Ullrich and Fremerey-Dohna, 1953). Only one report (Weyers, 1954) specifically mentions absence of nanism. This nanism is accompanied with

a retardation in skeletal development (personal observation).

(4) Hypotrichosis was seen in all cases except that reported by Nizetic (1954). It also affects the axillary and pubic hair (Lefertstra, 1956; personal observation), but it chiefly affects the hairy skull, eyelashes, and eyebrows.

Hair growth is scanty, with thin light hair, sometimes whitish (Schondel, 1943; Gregory, 1955), and as a rule there is alopecia areata. The bald patches often are on the frontal aspect (Marchesani, 1949; Blodi, 1957, Case 21) and on the posterior and temporal surfaces of the skull (personal observation) or along the cranial sutures (sutural alopecia: Aubry, 1893; Bergmeister, 1911; Ullrich and Fremerey-Dohna, 1953; Weyers, 1954).

Eyebrows are scanty and sometimes completely lacking (Schondel, 1943, Case 3; Gregory, 1955; Blodi, 1957, Cases 20 and 21). Lashes are short, thin, scanty, and sometimes also lacking (Schondel, 1943, Case 3; Moehlig, 1946; Weyers, 1954).

(5) Atrophy of the skin is as a rule localized to the head, where the skin is thin, white, dry, soft, taut, sclerous, and veined (Aubry, 1893; Schondel, 1943, Cases 3 and 4; Moehlig, 1946; Weyers, 1954; Gregory, 1955; Gregersen, 1956; Blodi, 1957).

The atrophy of the skin is particularly marked on the nose, where it is often localized (Schondel, 1943, Case 4; Hallermann, 1948, Cases 6 and 7; Streiff, 1950; Ludwig and Korting, 1950; Ullrich and Fremerey-Dohna, 1953; Nizetic, 1954; personal observation).

Hallermann (1948, Case 7) mentioned numerous skin folds in the face. Ludwig and Korting (1950) mentioned vitiligo of the trunk. Personal findings included lividness of the thighs and the popliteal hollows.

(6) Bilateral microphthalmia has been seen in 17 of 22 cases. It was not mentioned by Aubry (1893), Moehlig (1946), Nizetic (1954), and Gregory (1955, Cases 15 and 16). Its severity is variable, the corneal diameter varying from 7 mm. (Schondel, 1943, Case 4; Gregersen, 1956, Case 19) to 10 mm.

(7) Total or incomplete bilateral congenital cataract has been found in all cases except that described by Schondel (1943, Case 3), which showed sequelae of uveitis.

The patient described by Gregersen (1956, Case 19) showed no crystalline opacity at the age of 5, but at the age of 15 there was spontaneous absorption of the lens with membranous conversion of both lenses.

*Other Ocular Anomalies.*—Apart from microphthalmia and congenital cataract, other ocular anomalies have been mentioned, although these were less important or rarer, viz., blue sclerae (Schondel, 1943, Case 4; Moehlig, 1946; Ludwig and Korting, 1950; Weyers, 1954; Nizetic, 1954); distichiasis (Blodi, 1957, Case 20); ptosis (Ludwig and Korting, 1950); anti-Mongoloid slant of palpebral fissures (Ludwig and Korting, 1950; Ullrich and Fremerey-Dohna, 1953; Blodi, 1957, Case 20); indentation in the external one-third of the lower palpebral margin (Ludwig and Korting, 1950); atrophy of the iris (Ludwig and Korting, 1950); corneal bulging (Gregersen, 1956, Cases 18 and 19); amorphous retrolenticular membrane (Ludwig and Korting, 1950); posterior synechiae (Ullrich and Fremerey-Dohna, 1953); floating bodies in the vitreous (Weyers, 1954); increased intraocular tension (Gregersen, 1956, Case 19); changes in the ocular fundus: small disseminated pigmentations (Gregersen, 1956, Case 18), foci of chorioretinal atrophy (Streiff, 1950; personal observation), peripapillary choroid atrophy (Hallermann, 1948, Cases 6 and 7), cherry-red macula surrounded by a grayish zone (Nizetic, 1954), pale discs (Gregersen, 1956, Case 18); coloboma at the entrance of the optic nerve (personal observation).

In view of the diminished vision of the affected subjects it is not surprising that the majority show horizontal, rotatory, or pendular nystagmus and converging or diverging strabismus.

*General Symptoms.*—General symptoms have also been found in some of these pa-

tients, although they seem to be exceptional. They may include underdevelopment of the adipose tissue of the subcutaneous layer and the musculature (Schondel, 1943, Case 3); osteoporosis (Moehlig, 1946; Nizetic, 1954); hypogenitalism with or without cryptorchism (Ludwig and Korting, 1950; Nizetic, 1954); claw hands (Nizetic, 1954); syndactylism (Gregory, 1955, Case 16); coxalgia (Gregory, 1955, Case 16); platyspondylism (Nizetic, 1954); slight mental retardation (Moehlig, 1946; Nizetic, 1954); dysraphic changes, e. g., lordosis with or without scoliosis (Schondel, 1943, Cases 3 and 4; Ludwig and Korting, 1950; Nizetic, 1954); "winged" shoulder blades (Schondel, 1943, Cases 3 and 4; Nizetic, 1954); barrel chest (Nizetic, 1954); hypotrophy of the musculature of the shoulder girdle (Nizetic, 1954).

TABLE 1.—*Visual Acuity Values Attained*

| | Case | Visual Acuity | | Remarks |
|---|---|---|---|---|
| | | Left Eye | Right Eye | |
| Schondel (1943) | 4 | 1/20 | 1/20 | |
| Hallermann (1948) | 6 | 5/35 | 0 | Secondary glaucoma, corneal dystrophy |
| Hallermann (1948) | 7 | 1/100 | 1/20 | |
| Streiff (1950) | 10 | 0 | 0 | Secondary glaucoma |
| Nizetic (1954) | 14 | 1/10 | 5/10 | |
| Gregory (1955) | 15 | 6/36 | p. l | |
| Gregory (1955) | 16 | 1/10 | 1/100 | |
| Leffertstra (1956) | 17 | 1/300 | 5/10 | |
| Gregersen (1956) | 18 | 2/24 | p. l | |
| Gregersen (1956) | 19 | 1/24 | 1/18 | |
| Blodi (1957) | | 1/100→0 | 1/100→0 | Bullous corneal dystrophy; secondary glaucoma |
| Personal observation | 22 | 1/20 | 1/40 | |

## Functional Results Obtained by Cataract Operations

Congenital cataract such as is observed in the syndrome described consists, at least if complete, of liquefied crystalline masses, discission of which gives rise to escape of whitish milky fluid (Bergmeister, 1911; Ullrich and Fremerey-Dohna, 1953; Leffertstra, 1956; Gregersen, 1956; personal observation).

The functional results obtained by the operation are not excellent. This is not surprising in view of the concomitance of microphthalmia and, due to this very fact, anomalies of the whole of the eyeball.

Visual acuity values attained are given in Table 1.

Hallermann's first patient (1948) is an interesting case. The boy was submitted to discission of the left eye at the age of 7; the result was luxation of the crystalline lens into the anterior chamber; extraction was effected without loss of vitreous; subsequently corneal dystrophy developed so that vision did not exceed 5/35.

At the age of 3½ the right eye showed spontaneous absorption of the cataract, with persistence of a secondary cataract membrane, iris reaction, and formation of posterior synechiae. This resulted in secondary glaucoma requiring iridectomy. Subsequently corneal dystrophy developed, and vision was ultimately almost nil.

It must be pointed out that Gregersen (1956, Case 19) also observed spontaneous bilateral absorption of the lens.

## Pathogenesis

The syndrome described results from a developmental disorder which arises in the course of the fifth to sixth week (Ullrich and Fremerey-Dohna, 1953) or even in the seventh week of embryonic life (Hallermann, 1951). This disorder in development or differentation affects the ventral cephalic extremity and, therefore, is outlined in the ectoderm but also in the mesoderm.

## Heredity

Apparently there is no heredity. All cases described are unique, and no parental consanguinity was established. Yet these facts do not necessarily exclude a hereditary factor. This condition may involve either a recessive affection or—more probably—a mutation. Since the patients so far collected have not hitherto had any offspring, it is impossible to form any conclusion in this respect.

There is no sex-linked predominance (11 males as against 9 females).

### Relation to Ectodermal Dysplasias

This syndrome is part of the great chain of ectodermal dysplasias. It can be differentiated without difficulty from the following conditions:

(1) Anhidrosis with hypotrichosis and hypodontia (Siemens, 1929).

(2) Hypotrichosis with ungual dysplasia (Clouston, 1929).

(3) Incontinentia pigmenti (Bloch, 1926), characterized by spotted pigmental dermatosis, ocular malformations, hypodontia, changes in cranial hair growth of the Brocq type of pseudopelade, and sometimes also changes in the nails.

(4) Reticulate pigmental dermatosis (Franceschetti and Jadassohn, 1954), characterized by poikiloderma of the Thomson type and associated with telangiectases, and congenital or infantile cataract (onset at age 2 to 5), saddle nose, some degree of acromicria, hypogenitalism, sometimes alopecia of the hairy skull with lack of eyelashes or eyebrows, dystrophy of the nails, dental anomalies (Jäckli-Miescher, 1939-1940; Cole et al., 1945, 1951) and even nanism (Jäckli-Miescher, 1939).

The syndrome would seem to be related to progeria, which is an ectodermal dysplasia, and to dyscephalia.

Dyscephalia includes dyscrania, craniofacial dysostosis, and first-arch syndrome.

Dyscrania may be isolated (e. g., oxycephaly) or associated with other anomalies of the extremities (Apert's acrocephalosyndactylism) or of the clavicle (cleidocranial dysostosis).

Craniofacial dysostosis may be isolated (Crouzon's disease) or associated with anomalies of the limbs (Vogt's cephalosyndactylism).

The first-arch syndrome (François and Haustrate, 1954) comprises pure mandibular dysostosis, otomandibular dysostosis, and Franceschetti's mandibulofacial dysostosis (Table 2). It may be associated with anomalies of the limbs (acrofacial malformation, mandibular dysostosis with Hanhart's peromelia).

TABLE 2.—*Dyscephalia*

| | Various Forms of Syndrome |
|---|---|
| I. Dyscrania | 1. Simple dyscrania |
| | 2. Apert's acrocephalosyndactylism |
| | 3. Cleidocranial dysostosis |
| II. Craniofacial dysostosis | 1. Crouzon's disease |
| | 2. Vogt's cephalosyndactylism |
| III. First-arch syndrome | 1. Pure mandibular dysostosis |
| | 2. Otomandibular dysostosis |
| | 3. Franceschetti's mandibulofacial dysostosis |
| | 4. Acrofacial malformation |
| | 5. Mandibular dysostosis with peromelia |

The syndrome described is connected with the first-arch syndrome.

The following can be said about differential diagnosis between the syndrome described and progeria, on the one hand, and the chief types of dyscephalia, on the other.

*I. Progeria.*—Progeria (Hutchinson-Gilford disease [1904] or senile nanism) is characterized by the following symptoms.

(1) Early onset, at birth or within a few months of birth.

(2) Proportionate nanism (arrest of growth), associated with underdevelopment or atrophy of the adipose tissue of the subcutaneous layers or of the musculature, acromicria, dystrophy or atrophy of the nails, and osteoporosis, sometimes with spontaneous fractures.

(3) Dyscephalia: hydrocephalic cranium or at least a cranium much more developed than the face and the skeleton; prominent frontal tuberosities and parietal tuberosities; hypoplasia of the mandible with bird face; anomalies and partial absence of teeth; persistence of deciduous teeth.

(4) Generalized atrophy of the skin (geroderma): The skin is delicate, dry, wrinkled, parchment-like, often sclerodermal; the cranial skin is heavily veined; the physiognomy is that of senility.

(5) Hypotrichosis: Hair, eyebrows, and lashes are scanty, thin, short, silvery or white, and sometimes completely lacking.

(6) Premature arteriosclerosis ensuing at the age of 5 years and producing early apoplectic strokes.

TABLE 3.—*Differential Diagnosis of Ectodermal Dysplasias*

| | Dyscephalia with Parrot Face, Dental Anomalies, Nanism, Hypotrichosis, Atrophy of Skin, Microphthalmia, & Congenital Cataract | Progeria | Franceschetti's Mandibulofacial Dysostosis | Cleidocranial Dysostosis |
|---|---|---|---|---|
| Profile & physiognomy | Parrot face, microstomia | Bird face, aged aspect, microstomia | Fish face, macrostomia | Square head & facial hypoplasia |
| Cranium | Scapho- micro- & brachycephaly with dehiscent sutures | Hydrocephaly, prominent frontal tuberosities & parietal tuberosities | Normal | Brachycephaly or platycephaly |
| Eyes | Microphthalmia & bilateral congenital cataract | Normal | Anti-Mongoloid slant of palpebrae, palpebral coloboma, hypoplasia of malar bone | Normal |
| Superior aspect of face (nose) | Aquiline nose, hypoplasia of nasal bones | Curved nose, hypoplasia of nose & mandible | Greek profile, no hypoplasia of nasal bone but sometimes of maxilla | Saddle nose, flattening of zygomatous bones, maxillary hypoplasia |
| Inferior aspect of face (mouth) | Mandibular aplasia, vaulted palate, open bite, teeth partially lacking & badly implanted | Mandibular aplasia, vaulted palate, open bite, teeth anomalously implanted | Mandibular aplasia, vaulted palate, open bite, anomalous implantation of teeth, blind fistulae between buccal angle & ear | Mandibular hypoplasia, vaulted palate, dental anomalies |
| External ear | Normal | Normal | Various anomalies | Normal |
| Height | Nanism | Nanism | Normal | Normal |
| Hair growth | Hypotrichosis | Hypotrichosis | Normal | Normal |
| Skin | Atrophic, taut, & veined on head & nose | Generalized atrophy of skin; skin on head heavily veined | Normal | Normal |
| General anomalies | None | Premature arteriosclerosis, chronic arthritis, hypogenitalism, atrophy of adipose tissue, subcutaneous & muscular atrophy | None | Aplasia of clavicle, kyphoscoliosis, laxity of ligaments, anomalies of pelvis |
| Extremities | Normal | Acromicria, ungual anomalies | Normal | Normal |
| Etiology | Congenital, cause unknown, no apparent heredity | Onset during first few months of life; heredity not established | Congenital, irregularly dominant heredity with variable expressivity | Congenital, dominant heredity |

(7) Chronic arthritis with deformity of joints and limitation of their mobility.

(8) Hypogenitalism.

Whereas progeria has some symptoms in common with the syndrome described, other symptoms are markedly different: In our syndrome there is no atrophy of the subcutaneous adipose tissue or the musculature, there is no acromicria, and there are no nail changes; hydrocephaly is exceptional, microcephaly or brachycephaly being more frequently seen. The atrophy of the skin is not generalized but localized to the head; wrinkles are rare; hair is not white; there are no early arteriosclerosis and no arthritis deformans.

In no case of true progeria has there been any microphthalmia or congenital cataract. Yet cases of nanism are known in which the senile type of dwarfism is combined with pigmental retinopathy, constriction of retinal vessels, and pallor of the optic discs (Walsh, 1957).

Apart from cases of typical progeria, there are atypical cases (progeroidism). Cockayne (1936, 1946) and Neill and Dingwall (1950) reported on four familial cases of nanism with microcephaly, mental retardation, and muteness but showing no other craniofacial anomalies, particularly no aplasia of the mandible and no hypotrichosis. The patients showed atypical pigmentary retinopathy and dissemination of fine pigmented dust throughout the ocular fundus.

*II. Cleidocranial Dysostosis.*—This syndrome (Scheutauer syndrome, 1871; Marie-Sainton, 1897) is characterized by the following findings.

(1) Dyscephalia: brachycephaly or platycephaly (square head) with persistently open fontanelles and sutural dehiscence; anomalies of the face (saddle nose, flattening of the zygomatous bones, hypoplasia of the mandible and the maxilla, vaulted palate, dental anomalies).

(2) Unilateral or bilateral absence of the clavicle or aplasia of its external extremity, so that the shoulders may be brought together in front of the chest.

(3) Frequent association of kyphoscoliosis, retarded ossification, laxity of ligaments, absence of union of the symphysis, hypoplasia of the cotyloid spaces (congenital luxation of the hip, coxa vara), arachnodactylism, and nanism (Kahler, 1939).

(4) Manifest dominant heredity.

Differences between cleidocranial dysostosis and the syndrome described are marked.

*III. Franceschetti's Mandibulofacial Dysostosis.*—Some authors (Streiff, 1950; Nizetic, 1954; Blodi, 1957) have ranked my syndrome with Franceschetti's mandibulofacial dysostosis. It is true that there are some capital symptoms of the syndrome that I have just described (mandibular aplasia, vaulted palate, dental anomalies) and some occasional symptoms (anti-Mongoloid slant of the palpebral fissures, aplasia of the malar bone) which give some grounds for this notion.

I have established, however, that the two syndromes are different.

1. The dyscrania with its brachycephaly and sutural dehiscence, hypotrichosis, atrophy of the skin, nanism, microphthalmia, and congenital cataract are not found in mandibulofacial dysostosis.

2. Palpebral coloboma, blind fistulae between the buccal angle and the ear, and various anomalies of the external ear, which are characteristic of Franceschetti's syndrome, are not seen in my syndrome. Only Ludwig and Korting (1950) mentioned an indentation of the external one-third of the lower palpebral margin with aplasia of the malar bone.

3. Ocular anomalies in the case of mandibulofacial dysostosis are localized to the eyelids, while those in my syndrome affect the eyeball itself. My syndrome, moreover, shows general anomalies which are not seen in Franceschetti's syndrome.

*IV. Otomandibular Dysostosis.*—My syndrome should finally be differentiated from otomandibular dysostosis (François and Haustrate, 1954).

Otomandibular dysostosis is characterized by usually unilateral agenesis (sometimes bilateral) of the mandible, with malformation of the temporomaxillary joint and the external ear and atresia of the external auditory meatus, presence of supernumerary auricular cartilage or fistulae in a line extending from the buccal angle to the tragus, and frequent concomitance of fissural lesions (harelip, cleft palate, transverse facial cleft) and irregular implantation of teeth.

It should finally be pointed out that the mesoectodermal dysplasia which I have described is sometimes associated with dysraphic changes, as shown by the observations of Schondel (1943, Cases 3 and 4), Ludwig and Korting (1950), and Nizetic (1954).

## Summary

A new syndrome is described which constitutes a well-defined clinical entity, characterized by dyscephalia with dyscrania, mandibular aplasia and bird face, dental anomalies, nanism, hypotrichosis, atrophy of the skin, microphthalmia, and congenital cataract.

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# The Influence of Epinephrine and Phenylephrine on Intraocular Pressure

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The use of epinephrine and phenylephrine in the management of open-angle glaucoma is well known to ophthalmologists. Reports of clinical investigations on the influence of epinephrine and phenlyephrine on the intraocular pressure have frequently appeared in the international literature.[1-5] Thus far, none of these reports have mentioned that a significant rise in intraocular pressure could occur in open-angle glaucoma after the topical application of epinephrine or phenylephrine. We have found three patients in whom the pressure actually rose although the angles remained wide and open. The purpose of this paper is to present information concerning the various effects (on intraocular pressure, facility of aqueous outflow, and rate of flow) of epinephrine and phenylephrine topically applied to glaucomatous and to normal eyes.

## Procedures and Materials

The effects of epinephrine and phenylephrine individually were examined in 19 patients. Twelve had open-angle glaucoma, and seven were normal controls. Seven of the twelve glaucoma patients were selected for study because their intraocular pressure failed to fall or actually rose after administration of epinephrine or phenylephrine. The other five glaucoma patients had the more usual decrease in pressure with this treatment and were included for comparative purposes.

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Before the medications under test were administered, the intraocular pressure and the facility of outflow were measured by the method of Grant.[6] The angle of the anterior chamber was examined with a Koeppe gonioscopic lens. Several tonometer readings were performed in each case, and the tonographic and gonioscopic examinations were repeated one and one-half to two hours after administration of the drugs. The miotic therapy was discontinued for at least 48 hours prior to the examination, and the contralateral eyes served as controls in judging whether a real effect was obtained. One per cent epinephrine bitartrate and ten per cent phenylephrine hydrochloride were used in this investigation.

All measurements of intraocular pressure were made with the electronic Schiøtz tonometer (V. Mueller & Company) and expressed according to the 1955 calibration of the Committee on Standardization of Tonometers. All tonographic tracings were made on a Sanborn recorder. Facility of aqueous outflow (C) was calculated from the 1955 calibration of the Committee on Standardization of Tonometers; in calculating aqueous flow (F) the pressure in recipient veins was considered to be 10 mm. Hg.

In an attempt to evaluate the scleral rigidity, tonometric readings were often made with both 5.5 and 10.0 gm. weights. No consistent or significant abnormalities in scleral rigidity were observed.

## Findings

On the basis of the tonographic and gonioscopic findings, the results of this in-

TABLE 1.—*Intraocular Pressure in Open-Angle Glaucoma After Topical Application of Epinephrine or Phenylephrine*

| Patient | Medication | I. O. P.* | | C* | | F* | | Pupil Diameter, Mm. | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before | After | Before | After | Before | After | Before | After |
| A. Increased intraocular pressure | | | | | | | | | |
| 1 | 1% epinephrine O. D. | O. D. 22 | 38 | 0.10 | 0.01 | 1.20 | 0.28 | 3 | 5.5 |
| | | O. S. 17 | 17 | 0.12 | 0.11 | 0.84 | 0.77 | 2 | 2 |
| 1 | 10% phenylephrine O. D. | O. D. 21 | 34 | 0.09 | 0.03 | 0.90 | 0.72 | 3 | 6 |
| | | O. S. 16 | 18 | 0.11 | 0.12 | 0.66 | 0.96 | 2.5 | 2.5 |
| 1 | 10% phenylephrine O. U. | O. D. 27 | 54 | | | | | 3 | 7 |
| | | O. S. 24 | 46 | | | | | 3 | 6 |
| 2 | 1% ephinephrine O. U. | O. D. 22 | 23 | 0.18 | 0.23 | 2.16 | 2.99 | Aphakia | Unchanged |
| | | O. S. 23 | 29 | 0.19 | 0.16 | 2.47 | 3.04 | O. U. | O. U. |
| 2 | 1% epinephrine O. S. | O. D. 24 | 23 | | | | | | |
| | | O. S. 25 | 30 | | | | | | |
| 2 | 1% epinephrine O. D. | O. D. 22 | 23 | 0.21 | 0.23 | 2.52 | 2.99 | | |
| | | O. S. 25 | 27 | 0.17 | 0.18 | 2.55 | 3.06 | | |
| 3 | 10% phenylephrine O. U. | O. D. 22 | 29 | 0.14 | 0.05 | 1.68 | 0.95 | 2.5 | 7 |
| | | O. S. 25 | 37 | 0.10 | 0.05 | 1.50 | 1.35 | 3 | 8 |
| 3 | 1% epinephrine O. S. | O. D. 28 | 29 | 0.06 | 0.06 | 1.08 | 1.14 | 2 | 2 |
| | | O. S. 30 | 36 | 0.06 | 0.04 | 1.20 | 1.04 | 2 | 4.5 |
| B. Unchanged intraocular pressure | | | | | | | | | |
| 4 | 10% phenylephrine O. D. | O. D. 37 | 33 | 0.16 | 0.16 | 4.32 | 3.68 | 2.5 | 3 |
| | | O. S. 32 | 28 | 0.16 | 0.18 | 3.52 | 3.24 | 2.5 | 2.5 |
| 4 | 1% epinephrine O. D. | O. D. 30 | 26 | | | | | 2.5 | 3.5 |
| | | O. S. 29 | 25 | | | | | 2.5 | 2.5 |
| 5 | 1% epinephrine O. S. | O. D. 13 | 13 | | | | | 2 | 2 |
| | | O. S. 33 | 30 | | | | | 2 | 3.5 |
| 6 | 1% epinephrine O. D. | O. D. 25 | 27 | | | | | 2 | 5 |
| | | O. S. 22 | 19 | | | | | 2 | 2 |
| 7 | 1% epinephrine O. S. | O. D. 17 | 16 | 0.26 | 0.26 | 1.82 | 1.56 | 3 | 3 |
| | | O. S. 21 | 23 | 0.17 | 0.11 | 1.87 | 1.43 | 3 | 6 |

* I. O. P., intraocular pressure, millimeters of mercury; C, facility of aqueous outflow, cubic millimeters per minute per millimeter of mercury; F, rate of flow

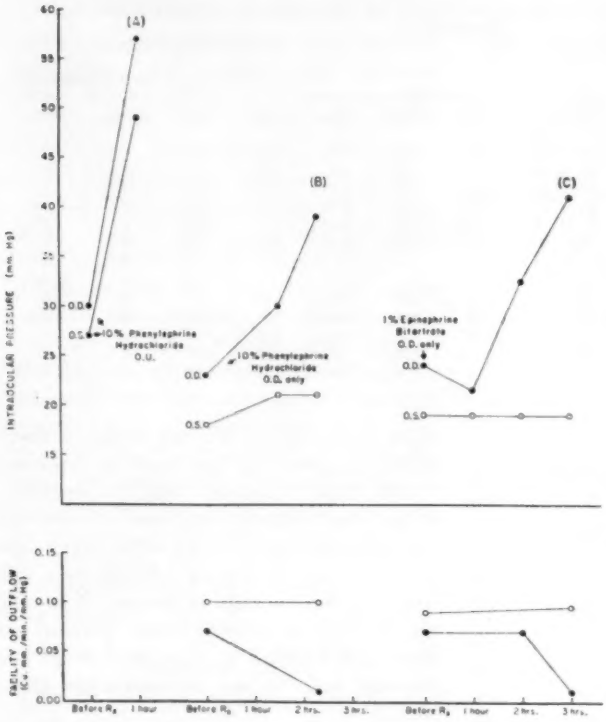
vestigation could be divided into the following groups:

1. *Glaucomatous Eyes.*—A. Increased or Unchanged Intraocular Pressure: Of the seven patients studied because epinephrine appeared ineffective in lowering the intraocular pressure, three showed an increased intraocular pressure and impairment of outflow facility after instillation of a single drop of epinephrine or phenylephrine (Table 1,*A* and Figure 1, *A*, *B*, and *C*). The other four patients exhibited no change in either intraocular pressure or facility of outflow with this treatment (Table 1,*B*).

It is interesting to note that in the same patients in which epinephrine produced a rise in intraocular pressure acetazolamide (Diamox) had its usual effect of lowering the tension. A significant increase in tension could be observed at about one to one and one-half hours after topical application of phenylephrine and at one and one-half to two hours after instillation of epinephrine. The increased intraocular pressure lasted for approximately four to six hours after these drugs were administered topically.

This type of increased resistance to outflow, however, is a reversible phenomenon. Although it may be maintained as long as the drug is administered, the impaired outflow facility will return to its original level spontaneously when the drug is discontinued. Also, the unfavorable increased resistance can be relieved by addition of 4% pilocarpine.

B. Decreased Intraocular Pressure: In the five patients with open-angle glaucoma who showed a considerable fall in intraocular pressure after instillation of epinephrine or phenylephrine, the facility of outflow did not change appreciably. The change in the rate of flow appeared to be




Black dot, treated eye; open circle, control eye. *A*, tension rise O. U. after topical application of 10% phenylephrine O. U. *B*, tension rise with concomitant further impairment of outflow facility in O. D. after topical application of 10% phenylephrine to O. D.; outflow facility is unchanged in control eye, O. S. *C*, tension rise with further impairment of outflow facility in O. D. after topical application of 1% epinephrine; tension and outflow facility unchanged in untreated control eye, O. S.

the key factor in lowering the intraocular pressure (Table 2).

2. *Normal Eyes.*—The seven normal eyes showed no significant change in intraocular pressure or in rate of flow after receiving topical epinephrine or phenylephrine (Table 3).

TABLE 2.—*Decreased Intraocular Pressure in Open-Angle Glaucoma After Topical Application of Epinephrine or Phenylephrine*

| | | I. O. P. | | C | | F | | Pupil Diameter, Mm. | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | Medication | Before | After | Before | After | Before | After | Before | After |
| 8 | 1% epinephrine O. S. | O. D. 24 | 23 | 0.17 | 0.20 | 2.38 | 2.60 | 3 | 3 |
| | | O. S. 27 | 21 | 0.20 | 0.18 | 3.40 | 1.98 | 3 | 6 |
| 8 | 1% epinephrine O. D. | O. D. 27 | 21 | | 0.16 | | 1.76 | 3 | 6 |
| | | O. S. 26 | 25 | | 0.16 | | 2.40 | 3 | 3 |
| 8 | 10% phenylephrine O. S. | O. D. 22 | 22 | | 0.16 | | 1.92 | 3 | 3 |
| | | O. S. 25 | 21 | | 0.18 | | 1.98 | 3 | 6 |
| 9 | 1% epinephrine O. S. | O. D. 18 | 18 | 0.20 | 0.19 | 1.60 | 1.52 | 3.5 | 3.5 |
| | | O. S. 32 | 21 | 0.25 | 0.24 | 5.50 | 2.64 | 3.5 | 4.5 |
| 9 | 10% phenylephrine O. S. | O. D. 18 | 17 | 0.20 | 0.21 | 1.60 | 1.47 | 3 | 4 |
| | | O. S. 28 | 18 | 0.26 | 0.27 | 4.68 | 2.16 | 3 | 8 |
| 10 | 1% epinephrine O. D. | O. D. 32 | 22 | | | | | 2 | 3.5 |
| | | O. S. 23 | 27 | | | | | 2 | 2 |
| 11 | 1% epinephrine O. S. | O. D. 22 | 22 | 0.13 | 0.13 | 1.56 | 1.56 | 3.5 | 3.5 |
| | | O. S. 29 | 17 | 0.12 | 0.16 | 2.28 | 1.12 | 3.5 | 5 |
| 12 | 1% epinephrine O. D. | O. D. 23 | 18 | 0.17 | 0.20 | 2.21 | 1.60 | 3 | 6 |
| | | O. S. 17 | 16 | 0.24 | 0.25 | 1.68 | 1.50 | 3 | 3 |
| 12 | 1% epinephrine O. S. | O. D. 22 | 22 | | 0.16 | | 1.92 | 3 | 3 |
| | | O. S. 17 | 17 | | 0.26 | | 1.82 | 3 | 3 |

TABLE 3.—*Normal Eyes Before and After Topical Application of Epinephrine or Phenylephrine*

| Patient | Medication | I. O. P. | | C | | F | | Pupil Diameter, Mm. | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before | After | Before | After | Before | After | Before | After |
| 13 | 1% epinephrine O.S. | O. D. 17 | 18 | 0.24 | 0.22 | 1.68 | 1.76 | 3 | 3 |
| | | O. S. 18 | 17 | 0.22 | 0.20 | 1.76 | 1.40 | 3 | 3.5 |
| 14 | 1% epinephrine O. S. | O. D. 16 | 13 | 0.30 | 0.43 | 1.80 | 1.29 | 3 | 3 |
| | | O. S. 16 | 12 | 0.31 | 0.43 | 1.86 | 0.86 | 3 | 3 |
| 15 | 1% epinephrine O. S. | O. D. 17 | 15 | 0.33 | 0.42 | 2.31 | 2.10 | 3 | 3 |
| | | O. S. 17 | 14 | 0.34 | 0.49 | 2.38 | 1.96 | 3 | 3 |
| 16 | 1% epinephrine O. S. | O. D. 12 | 11 | | | | | 3 | 3 |
| | | O. S. 13 | 10.5 | | | | | 3 | 3.5 |
| 17 | 10% phenylephrine O. D. | O. D. 12 | 9 | 0.30 | 0.33 | 0.60 | | 3 | 6 |
| | | O. S. 13 | 12 | 0.23 | 0.23 | 0.69 | 0.46 | 3.5 | 3.5 |
| 18 | 10% phenylephrine O. U. | O. D. 18 | 17 | 0.27 | 0.27 | 2.16 | 1.89 | 3 | 8 |
| | | O. S. 15 | 16 | 0.31 | 0.33 | 1.65 | 1.98 | 3 | 8 |
| 19 | 10% phenylephrine O. S. | O. S. 15 | 16 | 0.25 | 0.28 | 1.25 | 1.68 | 3 | 6 |

## Comment

Two clinically useful sympathomimetic compounds, epinephrine and phenylephrine, have been previously noted to decrease intraocular pressure when applied topically to the eye.[7,8] It has been stated that these drugs lower intraocular pressure by decreasing the aqueous formation. The actual mechanism of action of these drugs on the secretory process has remained unknown.[9-11] These drugs have proved useful clinically for topical application with miotic therapy and carbonic anhydrase inhibitors in selected patients with open-angle glaucoma or secondary glaucoma. Serr (1925)[12] hypothesized that the vasoconstrictors, such as cocaine and epinephrine, decrease intraocular pressure in glaucomatous eyes by first decreasing the blood volume content of the globe and then diminishing the secretion of aqueous by a toxic effect on the ciliary epithelium. He also mentioned that by simultaneous use of epinephrine and miotics a marked lowering of tension can be brought about.

Epinephrine, when applied locally, may induce a twofold response, namely, a constriction of the small vessels of the iris associated with a fall in intraocular pressure followed by a marked engorgement of the vessels (Cristini, 1949), with a turgescence of the ciliary body and a small rise in the intraocular pressure (Larsson, 1932; Colle et al., 1931). This second effect may often escape attention, since it lasts a short time and gives way to a state of hypotony (Poos, 1931; Larsson, 1932). Generally, it has been accepted that both epinephrine and phenylephrine produce either no change or a small rise in tension followed by a fall when applied topically to the eye. It is said the increase in tension never amounts to more than 5 mm. Hg; thus, these drugs are reported safe to use in open-angle glaucoma.[7,13]

We have found, however, that in occasional patients with open-angle glaucoma there is a significant and prolonged rise in intraocular pressure following topical administration of epinephrine or phenylephrine. This occurs in the absence of any gonioscopically visible changes in the angle, although tonographic data show the tension rise to be due to further impaired outflow facility. The mechanism of this outflow impairment is unknown. The knowledge that such a tension rise is possible is of obvious importance in the management of glaucoma, especially in one-eyed patients or those with advanced glaucoma.

In patients benefited by epinephrine or phenylephrine our findings are in agreement with Goldmann's, Weekers', and Becker's reports, i. e., the fall in tension is due to decreased rate of aqueous production.

## Summary

Clinical investigations have been made of the influence of epinephrine and phenyleph-

rine upon the intraocular pressure in both normal and glaucomatous eyes. It has been found that a fall in intraocular pressure induced by these drugs in open-angle glaucoma is due to a decrease in the rate of aqueous flow. In occasional cases has been noted a significant rise in intraocular pressure with additional impairment of outflow facility in open-angle glaucoma following topical application of epinephrine or phenylephrine, despite the fact that the angles remained wide and open. In other instances it has been noted that these drugs individually had no evident beneficial effect. In managing eyes with open-angle glaucoma, particularly in advanced cases or in one-eyed patients, the possibility of the intraocular pressure being increased should be kept in mind. This hazard appears to be less if miotics are employed simultaneously.

Drs. W. Morton Grant and Robert Trotter gave aid and suggestions in this investigation.

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# The Fine Structure of the Lens Epithelium

*An Electron Microscopic Study*

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## Introduction

Improved techniques of fixation and ultrathin sectioning in electron microscopy now permit the study of biological tissue on a nearly molecular level and in its natural milieu; as a result, a great amount of new information is available to cytologists.

The lens epithelium was selected for the present investigation because of its important role in the biology of both the normal and the pathological lens. A variety of functions is combined within this monolayered structure, as can be presumed from the morphological differentiation into a "resting" (central) zone and a "germinative" (equatorial) zone. Another interesting aspect is that the mature lens, although devoid of any nervous and vascular supply, constitutes an organelle with continuous cytokinetic activity.

Previous electron microscopic studies on the lens have been primarily concerned with the capsule (Bahr,[1] Bairati and Grignolo,[2] and Grignolo[3]), zonular fibers (Böke and Lindner[4]), and lens fibers (François, Rabaey, and Vandermeerssche[5]) and were carried out on homogenized, chemically prepared, and sectioned material. The present study deals with lens epithelia of adult rats, guinea pigs, rabbits, and monkeys that were selected in order to obtain comparative material from various species and to establish an electron microscopic pattern corresponding to normal conditions.

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## Material and Methods

In this study 4 guinea pig lenses, 6 rat lenses, 10 rabbit lenses, and 6 monkey lenses were examined. Adult guinea pigs (600 to 720 gm.), rats (180 to 240 gm.), rabbits (1.7 to 2.3 kg.), and Macaca mulatta (rhesus) monkeys (2.5 to 3.5 kg.) were anesthetized with pentobarbital (Nembutal) (30 mg. per kilogram); in addition, 1 cc. of 2% lidocaine (Xylocaine) was injected retrobulbarly. The lens was then removed from the eye and immediately immersed in a solution of 1% osmium tetroxide buffered with barbital (Veronal) acetate at pH 7.4 (Palade[6]). The lenses were fixed for a time ranging from one to three hours at room temperature, subsequently washed in the buffer solution, and rapidly dehydrated in a graded series of ethyl alcohols.* Pieces of the anterior capsule with epithelium of approximately 1 mm. in diameter were excised during dehydration. Occasionally, cortical lens fibers adhered to the preparation. The specimens were selected from various regions, that is, from central, intermediate (preequatorial), and peripheral (equatorial) zones. They

* This procedure gave the best and most constant results, as was determined by a series of experiments in which the following factors were systematically varied: concentration of osmium tetroxide; time and temperature of fixation; tonicity of the fixative; initial fixation of the tissue by infusion into the anterior chamber, with or without previous injection into the lens; secondary impregnation with phosphotungstic acid; dehydration time; dehydrating agents such as methanol and dioxane; polymerization temperature, and concentration of initiator and step at which it was added.

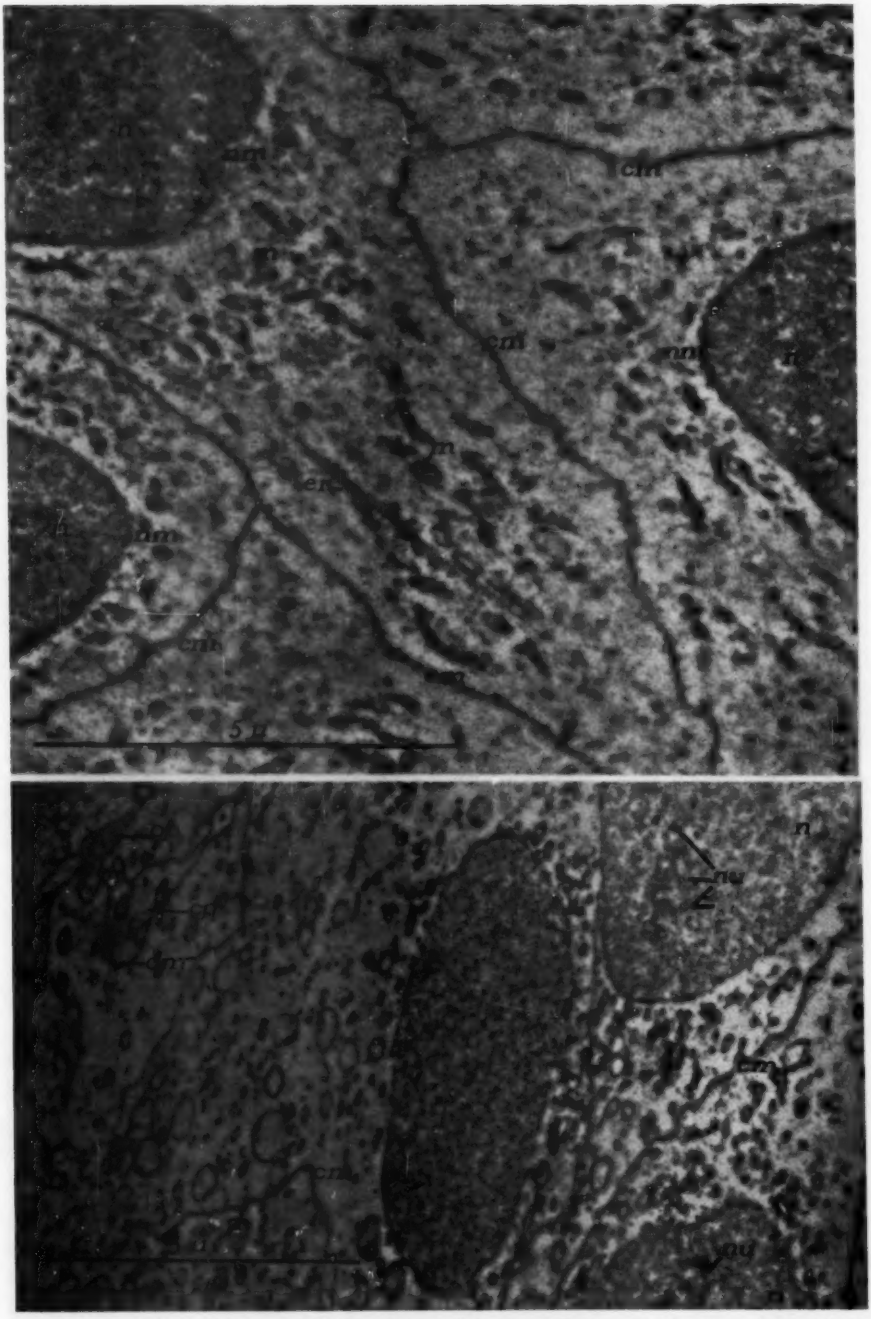
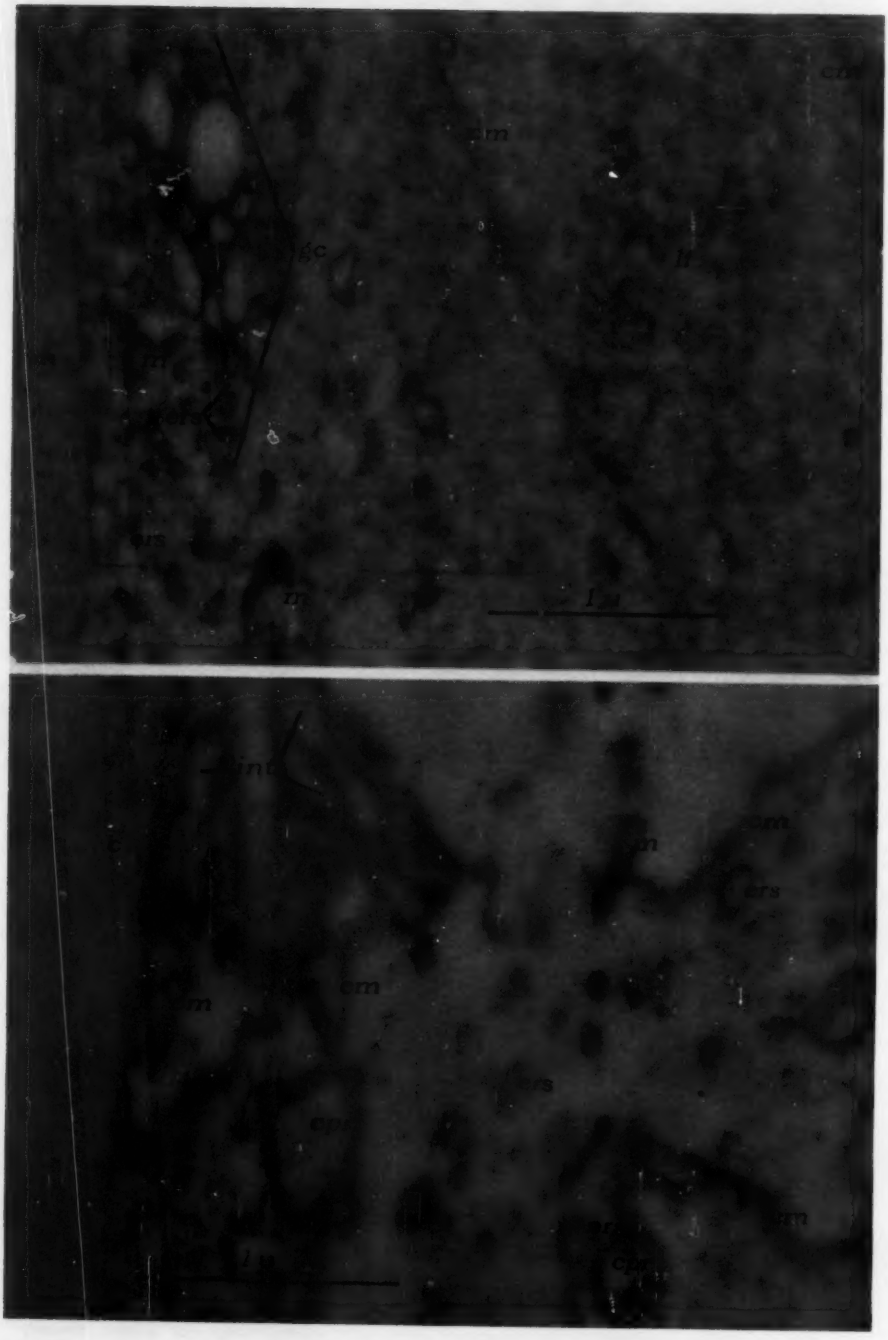



Fig. 1.—Guinea pig lens epithelium, intermediate zone. In the slightly tangential section, parts of five cells are separated by densely outlined cell membranes (*cm*). Portions of three nuclei (*n*) are surrounded by their nuclear membranes (*nm*) in this wide-field picture taken at a relatively low magnification. Mitochondria (*m*) and endoplasmic reticulum (*er*) can be identified in the cytoplasm. Approximately × 13,400.

Fig. 2.—Rabbit lens epithelium, equatorial zone, in a slightly tangential section through capsule (*c*) and epithelium. Tortuous cell membranes (*cm*) outline the cytoplasm of individual cells. In the vicinity of the capsule a considerable number of cross sectioned (*cp*) and obliquely-cut (*op*) cell processes are in the plane of the section. Nucleolar structures (*nu*) appear in two nuclei (*n*). Approximately × 10,000.



were then embedded in a mixture of prepolymerized butyl and methyl methacrylates in the ratio of 9:1, at 65 C, and with 1.5% of the initiator, benzoyl peroxide, added before prepolymerization. Sections of adequate thickness were cut on a Servall-Porter-Blum microtome and transferred to collodion-carbon-filmed grids. They were examined in an RCA electron microscope, Model EMU-3C with standard equipment. Photographs were taken at magnifications ranging from 3400 to 21,500 and optically enlarged from 3 to 10 times.

## Observations

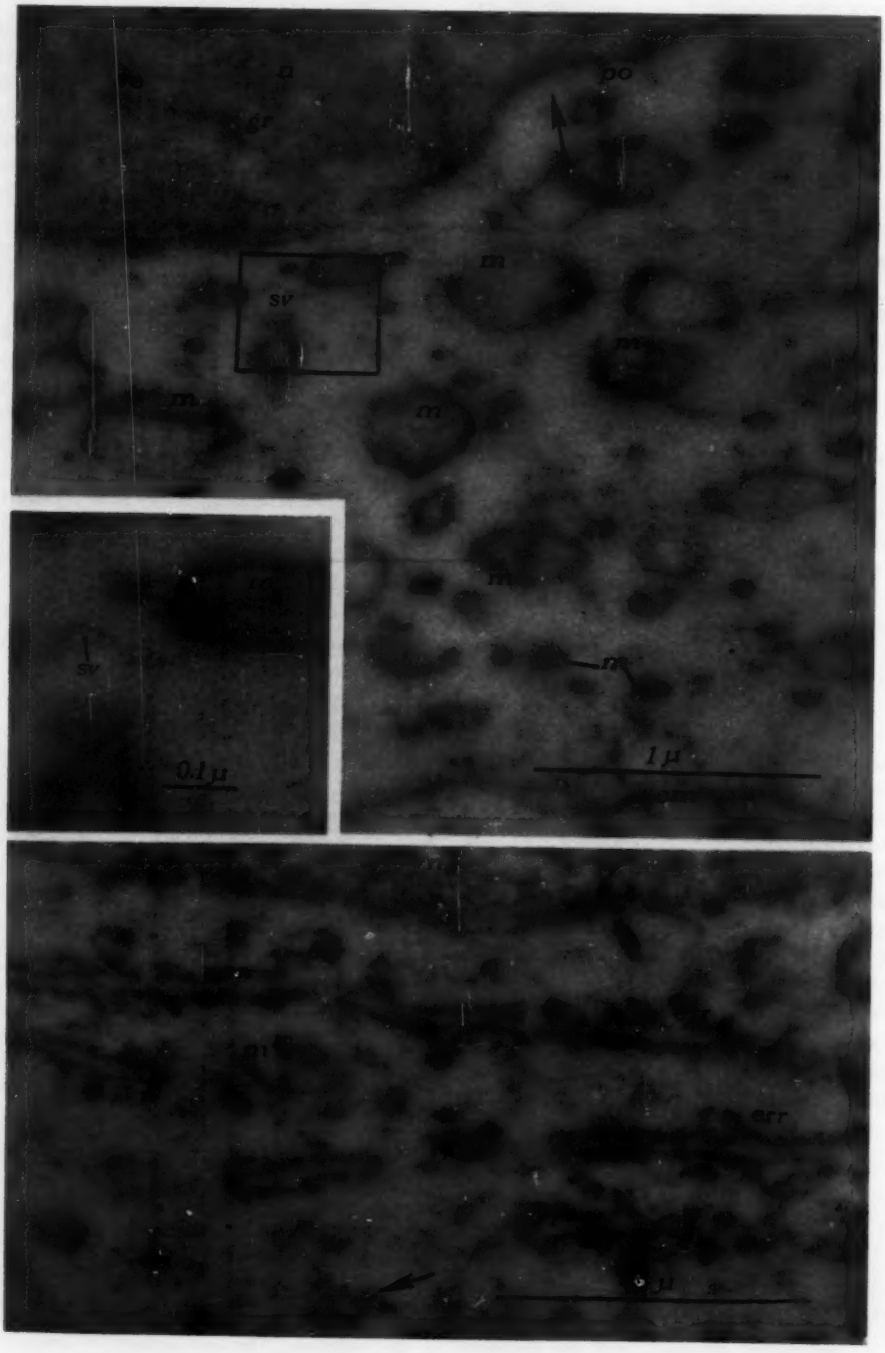
The general cytoarchitectural relationship between epithelial cells, capsule, and lens fibers, as seen in the electron microscope, is the same in the four species studied. The monolayered epithelium is interposed between the lens capsule and the youngest fibers of the cortex in the anterior half of the lens. The individual epithelial cell (Figs. 1, 2, and 3) in the section is outlined by its cell membrane, represented by a continuous dense contour of about 60 A. thickness. A less-opaque space of about 80 A. separates it from the parallel membrane of the adjacent cell (Fig. 5) or lens fiber. The boundary against the lens capsule consists solely of the anterior epithelial-cell membrane (Fig. 4). Under the preparative conditions of the present study, the adjacent capsular region is relatively homogeneous (Fig. 4), containing occasionally recognizable filamentous elements. The line representing the anterior cell membrane appears rather straight, in contrast to the membranes of neighboring cells or fibers which are irregularly outlined and exhibit signs of interdigitating cell processes (Fig. 4). These interdigitations increase in number toward the capsule (Fig. 2). At the border of two cells, profiles of circular or oval double membranes which sometimes contain cytoplasmic material are frequently encountered, thus indicating cross sectioned interdigitations (Fig. 4). They can be observed especially in sections which are cut in a plane tangential to the anterior lens surface. The irregular shape of the cells, with their numerous processes and interdigitations, is observable in all regions of the lens epithelium. It is perhaps more pronounced in the equatorial zone. In only a few instances does the intercellular border near the capsule show a regular, straight course. The continuity of the anterior part of the cell membrane is sometimes interrupted by openings of about 47 A. (Fig. 7).

The various intracellular structures appear similar in the species studied, although there are certain differences in organization and quantity within the individual zones of the epithelium. The various cell constituents are described in detail and the zonal differences are pointed out below.

*Nucleus.*—The main portion of the nucleus in the lens epithelial cell is usually located in that part of the cell which is adjacent to the cortex. The nucleus is round or ovoid, and its periphery, outlined by two dense lines, may show indentations (Fig. 5). The nuclei are more opaque than the surrounding cytoplasm and contain resolvable granular or vesicular-like formations which possess no obvious organizational pattern. Occasionally, the nuclear envelope is discontinuous. In this case, the two parallel lines of the nuclear membrane join each

Fig. 3.—Monkey lens epithelium, central zone. A cell membrane (*cm*) separates the posterior part of the cell with part of a nucleus (*n*) from the adjoining lens fiber (*lf*). Another cell membrane (*cm'*) indicates the boundary of two lens fibers. In the cytoplasm of the epithelial cell, a Golgi complex (*gc*) and mitochondria (*m*) can be distinguished. Oval profiles of smooth-surfaced endoplasmic reticulum (*ers*) are connected with the Golgi complex; granules (ribonucleoprotein) are attached to the outer nuclear membrane. Approximately × 36,000.

Fig. 4.—Rat lens epithelium, peripheral zone. An area comparable to the anterior cell portion in Figure 2 shows numerous cell processes (*cpr*) with interdigitations (*int*) outlined by cell membranes (*cm*). Mitochondria (*m*) and mostly oval profiles of the smooth-surfaced endoplasmic reticulum (*ers*) are distributed in the cytoplasm. The lens capsule (*c*) seems homogeneous. Approximately × 40,000.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other, leaving a very small breach, of an average size of 320 A., which has been interpreted as a nuclear pore by some authors (Figs. 5 and 8).

Nucleoli can be observed as irregularly formed densities within the body of the nucleus (Fig. 2). They frequently seem to consist of resolvable clusters of a dense granular material.

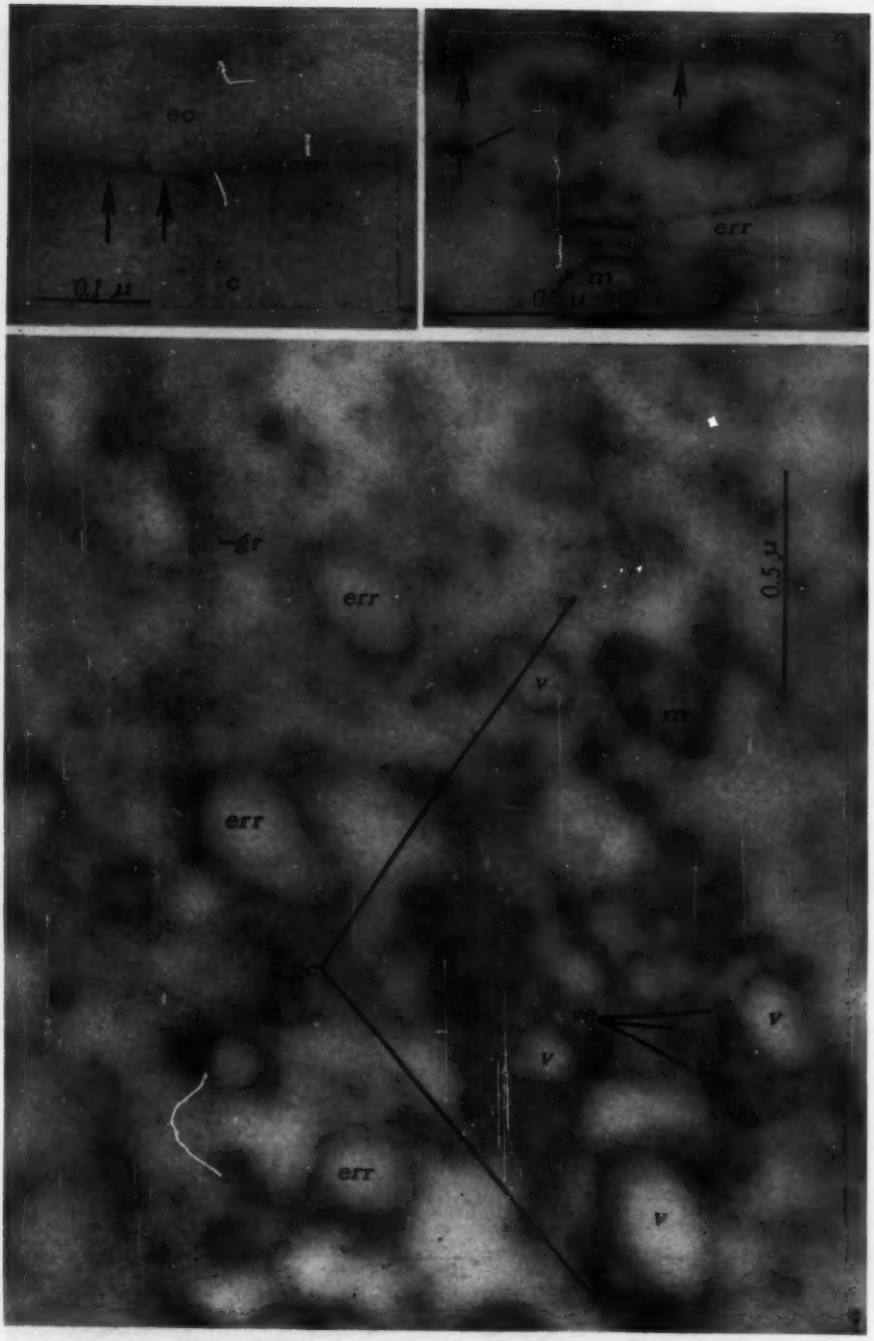
*Mitochondria.*—Sectioned mitochondria are dispersed throughout the entire cytoplasm of the epithelial cells, without definite regional differences in shape or size (Figs. 5, 8, and 9). The single element appears as a round or ellipsoid profile with a boundary of two dense lines each 50 A. thick and approximately 55 A. apart, thus representing a double membrane. The mitochondria vary in length from 0.14$\mu$ to 0.65$\mu$. The inner organization is characterized by a few transverse double membranes (cristae mitochondriales) with a spacing of about 55 A. Depending on the plane of the section, the cristae occasionally form circular profiles or infoldings or inwardly directed tubules of the inner limiting membrane. The cristae are either distributed at random or are oriented in the direction of the longer axis. The mitochondral ground substance appears homogeneous but is somewhat more opaque than the surrounding cytoplasmic matrix. The number of mitochondria seems to differ in the various regions of the epithelium. In the equatorial zone they form the preponderant cytoplasmic element (Fig. 5), but they are less frequently encountered in the intermediate (Fig. 6) and central zones (Fig. 3).

*Endoplasmic Reticulum.*—"Endoplasmic reticulum" (Porter and Thompson,[7] Porter and Kallman,[8] and Palade[9]) refers to those membranous cytoplasmic structures which are present in a considerable number of biological tissues and are clearly resolved in electron micrographs. The term is synonymous with "ergastroplasm" (Bernhard, Gautier, and Oberling[10]) and "double membrane system" (Sjöstrand[11]). In a three-dimensional arrangement, it probably forms a reticular system within the cell. The formation includes two types which have in common a double membranous or vesicular-like structure. The "rough"-surfaced endoplasmic reticulum has granules on the outer side of these membranes, while the "smooth" endoplasmic reticulum is agranular. The granules are considered to represent ribonucleoproteins (Palade[12]).

In the lens epithelium the rough-surfaced endoplasmic reticulum appears in a number of persistent organizational patterns (Fig. 10). One type is characterized by an aggregation of closely spaced, double membranes arranged in one to four parallel rows which in some cases extend for 3.4$\mu$ (Fig. 10*a*). The other type consists of elongated or vesicular profiles which occur in somewhat random arrangement (Fig. 10*b*). The granules of the endoplasmic reticulum have a diameter from 100 to 200 A. and are found either associated with membranes or grouped in clusters close to the outer nuclear membrane (Fig. 3). Sometimes they are dispersed in the cytoplasmic matrix without visible attachment to membranes.

Fig. 5.—Rabbit lens epithelium, equatorial zone. This micrograph provides information on the number and organization of mitochondria (*m*) peculiar to this region. The mitochondria are bounded by double membranes and contain a few cristae. Smooth-surfaced endoplasmic reticulum and profiles of a small vesicular component (*sv*) in the ground substance are seen in the cytoplasm. The nucleus (*n*) is indented (arrow), and the nuclear membrane is interrupted by a pore-like formation (*po*). The nucleoplasm includes a few vesicular (*ve*) profiles and granules (*gr*). One cell boundary is visible (*cm*) at the bottom of the figure. Approximately × 43,000. The insert (5*a*) shows on an enlarged scale the small vesicular component (*sv*) in the ground substance. A mitochondrion appears at *m*. Approximately × 107,500.

Fig. 6.—Guinea pig lens epithelium, intermediate zone. The rough-surfaced endoplasmic reticulum (*err*) consists of membranes with attached granules. Such granules (ribonucleoprotein) can also form clusters without apparent association with membranes, as indicated by the arrow. A cross sectioned mitochondrion (*m*) and part of a nucleus (*n*) are present in the cytoplasm. Approximately × 48,000.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The type of endoplasmic reticulum characterized by a disposition in parallel rows is not frequently seen in the lens epithelium. When observed, it is located exclusively in cells of the central and intermediate zones, not only in the perinuclear region of the cell (Fig. 6) but also in the ectoplasm (Fig. 1).

The elongated or vesicular type of endoplasmic reticulum (Fig. 8) is commonly found in cells of the central and intermediate zones, but it can appear in the peripheral region as well. In most instances, it is diffusely scattered throughout the cytoplasm in all zones; occasionally it is arranged in groups.

The smooth-surfaced or agranular type of endoplasmic reticulum presents either elongated or vesicular profiles (Fig. 10*c*) which are distributed either at random or in loose aggregates (Fig. 3). This type occurs predominantly in the peripheral and intermediate zones.

In all the species studied the appearance, arrangement, and distribution of the endoplasmic reticulum are analogous.

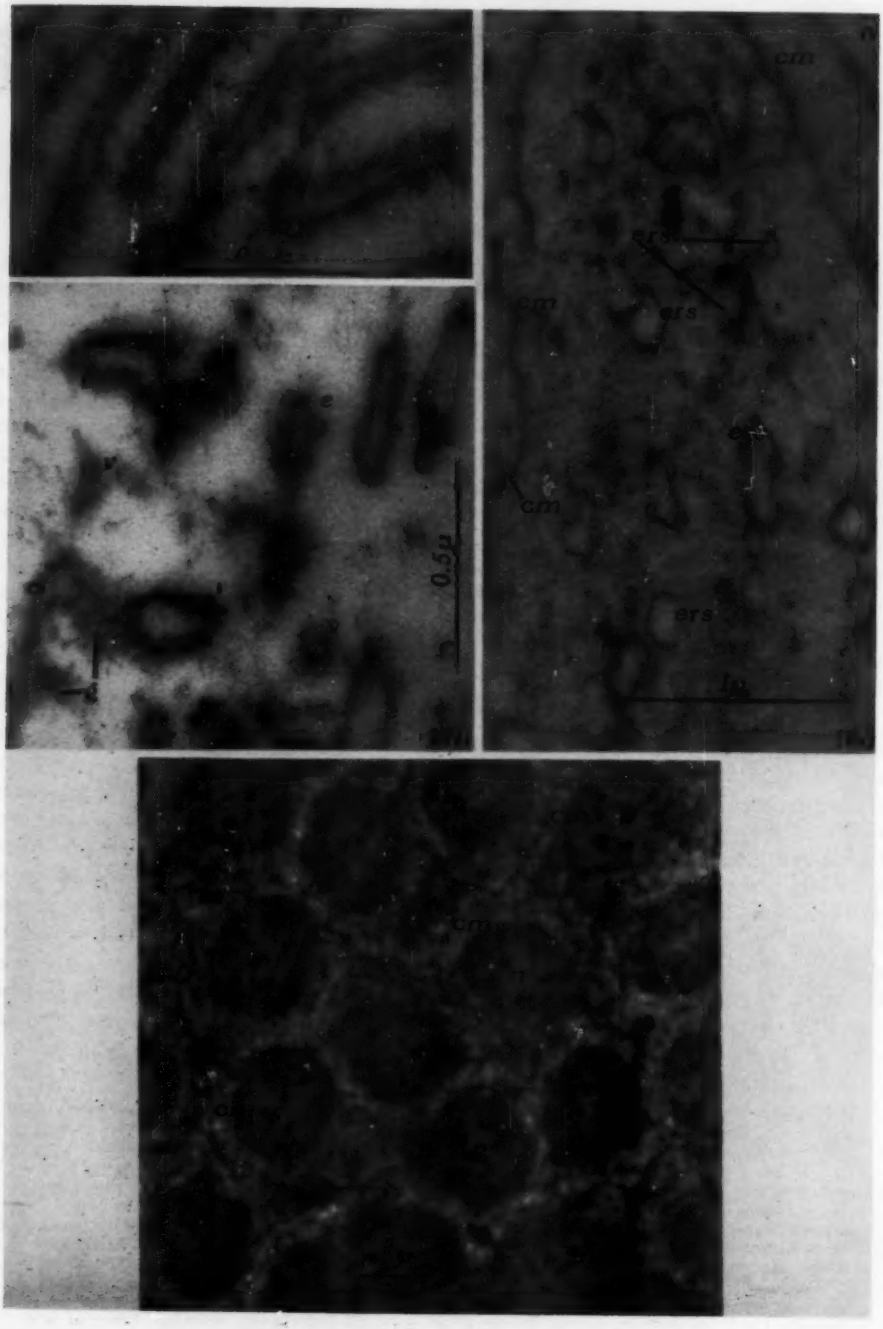
*Golgi Complex.*—The electron microscopic equivalent of the Golgi complex has been identified in several animal cell types. It consists of a congregation of vacuoles, smooth double membranes, and granules (Dalton and Felix [13]). In the lens epithelium the Golgi complex is commonly located in the vicinity of the nucleus (Fig. 3) within that portion of the cell which is adjacent to the lens fibers. In any single cell, more than one such structure may be seen. The complex is composed of a few vacuoles surrounded by elongated, smooth profiles and by vesicles which vary in diameter and density. It is embedded in the cytoplasmic matrix and is not outlined by any sort of limiting structure (Fig. 9). Some of the elements within the complex appear to extend into the endoplasmic reticulum and may be components of it. The distribution, location, and composition of the Golgi complex are similar in all species studied.

*Cytoplasmic Ground Substance.*—This term usually refers to the matrix, in which the formed and resolvable cytoplasmic elements are embedded. In addition to those constituents already described, there exists a component of the lens epithelial cell which resembles fine filaments under low magnification (Fig. 5). This structure is slightly denser than the matrix and shows no distinct pattern of organization. It is dispersed at random through the region of the cytoplasm between nucleus and capsule and, less frequently, in the posterior half of the cell. Higher magnifications reveal a double-membrane structure with a constant distance between the dense contours. It may assume an elongated, oval, circular, or semicircular profile (Fig. 5*a*). Variations in shape and size probably depend on the plane of sectioning. Thus, elongated profiles may alternate with round, vesicular elements, but the structureless space between the double membranes remains rather constant at 45 A., while the width of the surrounding membrane is about 30 A. The density of these profiles scarcely differs from that of the surrounding cytoplasm. No further details can be resolved with the technique presently employed.

Fig. 7.—Rat lens epithelium and capsule, peripheral zone. The anterior cell membrane (*cm*) of the epithelial cell (*ec*) is in immediate contact with the lens capsule (*c*). Arrows point to the openings in this boundary which are suggestive of stomata. Approximately × 183,000.

Fig. 8.—Rabbit lens epithelium, intermediate zone. The upper marginal portion of the figure shows part of a nucleus (*n*) and its membrane (*nm*), consisting of two dense lines with a less-opaque space between them. Pore-like formations in the nuclear membrane are indicated by arrows. An elongated profile of the rough-surfaced endoplasmic reticulum (*err*), mitochondria (*m*), and small vesicular components of the ground substance (*sv*) can be resolved in the cytoplasm. Approximately × 86,000.

Fig. 9.—Monkey lens epithelium, equatorial zone. Vacuoles (*v*) together with smooth-surfaced, elongated (*e*), and vesicular elements (*ve*) of various densities constitute the Golgi complex (*gc*). In addition, profiles of the rough-surfaced endoplasmic reticulum (*err*) as well as a mitochondrion in cross section are visible. Approximately × 70,000.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## Comment

Electron microscopic studies of the lens epithelial cell reveal an irregularly shaped cell with numerous processes and interdigitations. These two characteristics might allow for the plasticity which is necessary during accommodation periods and which enables the cell to remain intact throughout its various deformations. It is, therefore, difficult to describe a "normal" cell shape. No attempt has been made to correlate the cell form and state of accommodation. Preparation techniques, particularly the knife impact, may also result in gross distortion of the cell shape.

The presence of structures suggestive of stomata in the cell membrane beneath the capsule may be significant, since analogous openings of somewhat larger dimensions have been described by Hall [14] and Pease [15] in cells of the liver and kidney capillary endothelia. The lens is an organelle which has no vascular supply, and its nutrition is dependent upon the exchange of metabolites between the lens and surrounding aqueous humor. Thus, the anterior cell membrane may be engaged in surface activity comparable, in some ways, to that of certain capillary endothelia.

Little new information can be gathered from the electron microscope studies on the nucleus of the lens epithelial cell. The presence of a double-membrane envelope with pore-like formations (Watson [16]) is a common finding. The outer limiting membrane of the nucleus has been regarded as a part of the endoplasmic reticulum (Watson [17]). The occasional attachment of small granules to it indicates a similar relationship in the lens epithelium.

In this investigation, no mitotic figures were noted. This can be explained by the fact that the ratio of mitoses to interkineses is very low. In the germinative layer of the rabbit it is estimated to be 60:100,000 cells (von Sallmann [18]). The chance of encountering one of these cells in an ultrathin section is, therefore, very slim. In order to obtain more data on nuclear structures, variations in the present technique will have to be employed.

The mitochondria seen in the lens epithelium are characterized by a double membranous boundary and internal cristae and correspond to the basic pattern as described by Palade [19,20] and Sjöstrand.[11] In comparison with those of several other tissues they are relatively small, regardless of the plane of section. It should be noted that the number of mitochondria per cell gradually increases from the central toward the germinative zone of the epithelium, although size and shape of these cytoplasmic constituents apparently remain unchanged.

The endoplasmic reticulum is scanty in amount and differs in local distribution in the individual zones of the epithelium. In general, it is preponderant in the central and intermediate zones. The smooth-surfaced type is found predominantly in the peripheral area, whereas the rough-surfaced variety, characterized by an arrangement in parallel rows, occurs almost exclusively in the central and intermediate

Fig. 10.—This composite illustrates the various types of the endoplasmic reticulum in the lens epithelial cells. (*a*) Rabbit lens epithelium, intermediate zone. The rough-surfaced endoplasmic reticulum is arranged in parallel rows. Approximately × 64,500. (*b*) Rabbit lens epithelium, intermediate zone. Rough-surfaced endoplasmic reticulum of the elongate (*e*) and vesicular (*v*) types shows a somewhat random arrangement. The structures in the lower left corner demonstrate the influence of the plane of sectioning upon the profiles of these elements. Thus, a single continuous component can appear vesicular (*v'*) or elongated (*e'*) or as an accumulation of granules (*g*) superimposed upon a tangentially cut portion of the membrane. Approximately × 62,200. (*c*) Monkey lens epithelium, central zone. The smooth-surfaced type of endoplasmic reticulum (*ers*) is scattered through the cytoplasm in the form of elongate and oval elements. This micrograph also shows cell membranes (*cm*) and part of the lens capsule (*c*). Approximately × 36,000.

Fig. 11.—Rat lens epithelium. Phase-contrast photomicrograph of a whole mount fixed with osmium tetroxide. Irregular membranes (*cm*) outline the cells. Granular material of various densities is resolved in the cytoplasm. Reichert-Zetopan phase contrast; × 700, photographically enlarged three times.

zones. Finally, the rough-surfaced, elongated, and vesicular profiles are visible in all three zones of the epithelium, gradually decreasing in amount from the central to the equatorial region. It is reasonable to assume that this variance in arrangement, distribution, and shape of endoplasmic reticulum and the difference in the number of mitochondria in these three zones are morphological expressions of differences in the biological functions of the cells within the lens epithelium.

The Golgi complex retains its morphological characteristics throughout the epithelium and is usually located in the centrosphere. There is a paucity of lamellar elements, but in general it bears close similarity to structures described in other tissues (Dalton and Felix[21]).

The small vesicular structure described as filamentous at low magnification possibly constitutes a cytoplasmic component peculiar to lens epithelium. It can be distinguished from the smooth-surfaced endoplasmic reticulum by the thickness and spacing of the membrane and by the density of the enclosed area. This part within the membranes of the small vesicular component does not differ in density from the surrounding cytoplasm, whereas in the reticular formations it is less opaque than the ground substance.

Several observations made in this electron-microscope study have their correlate in numerous investigations carried out with the light microscope on stained, unstained, and histochemically treated lens epithelium. Cell processes were demonstrated with a silver technique as early as 1892 by Barabaschew,[22] and, after maceration, the presence of interdigitations was assumed (Hosch[23]). After silver impregnation, mitochondria were identified by Maggiore,[24] and with phase-contrast microscopy, by Böke[25] and Van den Heuvel.[26] Böke[25] successfully used Janus green stain for the same purpose and observed a greater number of mitochondria in the cells of the germinative zone. The presence of a Golgi apparatus was shown with the Aoyama silver technique by Baba.[27] Van den Heuvel[26] repeated this method and also employed osmium tetroxide and Sudan black as alternative stains. In the present study no attempt has been made to identify zonal differences in concentrations of deoxyribonucleic acid and of acid and alkaline phosphatase as Brolin and Lindstrom[28] demonstrated cytochemically in lens epithelium.

The endoplasmic reticulum in the lens epithelium is not visible in the light microscope for two reasons. First, the limited resolution does not permit a morphological differentiation between these structures and mitochondria, since their dimensions approach the maximal resolving power of the light microscope (Fig. 11). Second, there is a sparsity of ribonuclear protein granules in the lens epithelium; thus, basophilic staining cannot be accomplished (Palade[12]). The differences in the techniques employed preclude a meaningful comparison between the results published by Lindner and Böke[29] and those reported here.

## Summary

The electron-microscope investigation on the normal, mature lens epithelium of the rat, guinea pig, rabbit, and Macaca mulatta (rhesus) monkey did not reveal any significant differences among the four species.

The lens epithelial cell has an irregular shape, with numerous cytoplasmic processes which frequently interdigitate with neighboring cells and lens fibers.

Besides the nucleus, the following cytoplasmic constituents were observed: endoplasmic reticulum, Golgi complex, mitochondria, and a small vesicular component in the ground substance.

Varieties in spatial arrangement, distribution, and quantity of cytoplasmic constituents are described in detail, are discussed with respect to their possible physiological significance, and are compared with the structures seen in the light microscope.

This study was inspired and guided by Ludwig von Sallmann, M.D., and was undertaken as an extension of his research on the lens. Mr. L. L.

Caravaggio, M.S., gave help and advice in the dissection of lenses, and Mr. F. H. Meiller processed the photographic prints.

Ophthalmology Branch, National Institutes of Health (14).

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# Conjunctival Flaps in the Treatment of Corneal Disease with Reference to a New Technique of Application

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Frequently there comes a time in the course of serious corneal ulceration when medical treatment fails and the ophthalmologist must result to surgery. This is particularly true when the ulceration is of unknown cause or when there is no known specific medical treatment. The first surgical treatment employed is usually either chemical or thermal cauterization, and this is frequently followed by other procedures, such as paracentesis, Saemisch section, delimiting keratotomy, peritomy, and the application of conjunctival flaps. The increasing numbers of indolent herpetic ulcerations, many of which have been adversely influenced by excessive steroid therapy, present a problem of rehabilitation of temporarily disabled persons.

Dissected flaps of conjunctiva offer a valuable means of covering the ulcerated cornea either temporarily or permanently. I shall enumerate the corneal conditions for which they are most useful and shall describe the technique that I have used in applying them to the cornea.

Conjunctival flaps fashioned to cover corneal injuries and corneal disease have been used for many years. Their application was described by Schöler [1] in 1877; by Krebs [2] in 1878; by Kuhnt [3] in 1883; by Meyer [4] in 1892, and by Kuhnt from 1889 to 1906. Van Lint,[5] writing in 1912, is generally credited with popularizing their use, but he used them primarily to reinforce cataract sections. More recently, Beyers,[6] Green,[7] and Haik [8] have developed this subject, and their work has contributed to the use of flaps for corneal diseases as well as injuries.

When the present-day ophthalmic surgeon considers the application of a conjunctival covering to the cornea, he thinks in terms of older methods available, namely, a purse-string flap drawn over the corneal center or a hood type of flap consisting of conjunctiva and Tenon's capsule drawn over the cornea from one sector of the limbus. The latter type of flap is frequently loosened and further mobilized by incising conjunctiva and often Tenon's capsule so as to form a bridge flap. It has been my experience that purse-string flaps rarely remain in position for more than four days before the conjunctiva retracts to its original position. Hood flaps, though somewhat more lasting, rarely remain in place permanently and almost always retract in a few weeks or months. The nondissected fornix flap developed by Haik was not designed as a permanent corneal covering. It proved its worth in World War II, and certainly it has a place today in the emergency treatment of corneal lacerations.

### Benefits of Conjunctival Flaps

The reasons why conjunctival flaps are of benefit to ulcerated corneas are not fully understood. There may be, in fact, several reasons, including some that are speculative.

1. The corneal ulcer is protected by a flap from tears and other conjunctival secretions. This may be the most important factor, for corneal edema always occurs when the epithelium is lost or even slightly injured. Therefore, in all cases of corneal ulceration, except in some unusual ones frequently associated with glaucoma, the

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cornea is swollen with fluid dialyzed from the tears. It may be that these "waterlogged" corneas have a lessened resistance to infection and heal slowly.

2. A corneal peritomy is done. Even though all the blood vessels in a heavily vascularized cornea are not severed by doing even a complete peritomy, the superficial ones are. This in itself greatly favors healing, especially in those cases where many blood vessels are present.

3. Trauma is lessened. The cornea is completely protected from outside influences while it is under a total conjunctival covering. This includes tears themselves, as mentioned before. The influence of continuous winking of the lids has long been suspected to be a deterrent to corneal healing, and certainly this evil is removed by a total conjunctival flap. In addition, the cornea is protected from outside irritants, of which drying, dust, collyria, and ointment containing drugs are but a few.

4. Blood and blood serum are in direct contact with the ulcer. A broad bridge of conjunctiva over the entire cornea is, in effect, a highly vascular membrane with an excellent blood supply from both sides. Its posterior or "raw" surface comes in direct contact with the infected, ulcerated, and frequently devitalized cornea. Until healing is complete, the posterior surface of the conjunctiva supplies blood corpuscles, blood serum, and other tissue fluids to this part. It is highly probable that this exerts a healthy influence on healing.

5. A pericorneal neurectomy is accomplished. The nerve supply to the corneal periphery is cut by virtue of the complete peritomy done in this operation. Even though only 1 or 2 mm. of the corneal periphery is supplied by sensory nerves entering from the conjunctiva, it has been postulated by Verhoeff [9] that cutting these nerves exerts a favorable influence in neuropathic keratitis.

### Objections to Conjunctival Flaps

The objections to covering the entire cornea with conjunctiva may be similarly summarized.

1. The influence of tears on corneal healing may be to some degree a beneficial one. Tears contain much lysozyme. These advantages are eliminated by this type of surgical treatment.

2. The further progress of the corneal disease is temporarily obscured from view. Ordinarily nothing can be seen through the flap for one or two weeks. Then the pupil can be seen, and in six to eight weeks some corneal detail can be visualized. When healing is complete, the healthy parts of the cornea can easily be distinguished from corneal scars and infiltrations. Since the disease process is practically always arrested by the application of the flap, this objection is not particularly important.

3. The status of the pupil cannot be determined. If secondary iritis accompanies the corneal disease, the ophthalmologist must prescribe adequate mydriatics empirically to assure cycloplegia and mydriasis.

4. The presence of secondary glaucoma can only be determined by digital palpation.

5. This is an all-or-none operation. A real disadvantage to this procedure is that reoperation is difficult, if not impossible. A single buttonhole, even though minute, in that portion of the flap overlying the cornea rapidly enlarges and may defeat the purpose of the operation. Should the flap retract, as it always will do if not properly prepared and applied, it cannot be reapplied. The lower bulbar conjunctiva does not supply enough tissue for this operation.

6. Transient ptosis follows some flap operations. It disappears entirely if the operation is done in the prescribed manner. Permanent partial ptosis is usually due to inclusion of Tenon's capsule in the flap, inadequate mobilization of the lateral and medial attachments of the bridge, or a combination of both of these factors.

Nevertheless, the beneficial results from total conjunctivoplastic covering of the

cornea indicate that the advantages far outweigh the disadvantages.

### Usefulness of Complete Permanent and Semipermanent Conjunctival Flaps

Up to this time, conjunctival flaps have been used chiefly in the treatment of injuries, especially perforating wounds of the cornea. Before direct corneal suturing was made possible by improved needles and sutures, almost all perforating corneal wounds were treated by drawing a Van Lint or hood type of flap over the lacerated cornea after excision of any prolapsed uveal tissue. These flaps hindered the further escape of intraocular fluid or other contents, brought the wound edges together, and promoted healing. Unless the flap became adherent to the wound edges, it retracted spontaneously, usually within a week. Today, there is greater inclination to approximate the wound edges by direct sutures, although many ophthalmic surgeons finish the operation by covering the entire wound by a conjunctival flap. Haik has more recently introduced a "fornix flap" for this purpose. This ingenious method of bringing the fornix folds over the cornea without dissection has proved to be of great value, particularly in war-time ophthalmology. This flap was not designed as a permanent covering of the cornea.

### Corneal Conditions Benefited by Complete Conjunctival Covering

*Herpetic Ulcers.*—Certainly a relatively small number of corneal infections caused by the virus of herpes simplex require so radical a treatment.

A. Epithelial herpes (dendritic keratitis), when uncomplicated, is usually a benign disease. Although self-limited, it sometimes runs a prolonged course, which can be shortened by the timely and proper application of a chemical cautery such as tincture of iodine.[10]

B. Fascicular keratitis is a common complication of prolonged or repeated epithelial herpes.[11] It is extremely resistant to medical therapy. Whether or not a similar disease process affects the stroma after it becomes vascularized is subject to speculation, but it is very possible that it does. Conjunctival covering of the cornea is useful when fascicular keratitis is a prominent feature of the disease.

C. Stromal herpes with or without ulceration is the most serious complication of herpetic infection. It follows an attack of epithelial herpes in 5% to 15% of all cases. Its incidence is believed to be higher now than formerly, probably as a consequence of the expanded use of local steroid therapy. I have covered many of these corneas with permanent or semipermanent conjunctival flaps, with good results. Conjunctival flaps are especially beneficial in stromal herpes where ulceration is also present.

D. Neuroparalytic keratitis is a clinical entity which exhibits a characteristic discrete roundish or oval ulcer in the central cornea associated with complete or sometimes incomplete loss of sensation. It frequently follows operations on the Gasserian ganglion for trifacial neuralgia. Less commonly, it is a sequela of other traumas, tumors in the middle fossa, infections, or vascular accidents or is of unknown cause. The corneal picture seen in Riley-Day's syndrome is typical of neuroparalytic keratitis, hypesthesia and alacrimia being a fairly constant feature of the condition.

In herpes simplex the corneal anesthesia seems to have a great influence on the condition of the cornea. Hypesthesia is a well-known accompaniment of corneal ulcers caused by the virus of herpes simplex. The intensity of the hypesthesia depends on the severity of the attack, the number of recurrences to which any cornea has been subjected, and the duration of any one attack. It is a common clinical observation that hypesthesia increases as the disease persists. In certain cases the hypesthesia becomes so marked that the cornea becomes virtually anesthetic. The corneal defect then shows all the characteristics of the classical

neuroparalytic ulcer. Therefore, neuroparalytic keratitis may be considered the fourth variation or complication of herpes simplex corneae. Under these circumstances the ulcer is a trophic one. Rarely, if ever, is herpes virus demonstrable during this phase. These corneas do especially well when covered by a conjunctival flap for a prolonged period of time.

*Relapsing Erosions.*—This mysterious but most troublesome corneal disease varies enormously in its severity. Fortunately, most cases are mild and short-lived and respond to the accepted methods of treatment. Occasionally the disease persists in spite of every medical treatment and causes the patient almost complete disability. In such cases a complete conjunctival flap offers almost immediate relief from pain and prompt healing. The flap may be completely or partially removed after three or four months.

*Bullous Keratopathy.*—Regardless of cause, bullous keratopathy is one of the most distressing conditions which confronts the ophthalmologist. There is no medical treatment which offers the patient more than temporary relief of symptoms or improvement in vision. Keratoplasty is notoriously unsuccessful, since the graft almost always takes on the characteristics of the host cornea and becomes edematous and opaque. Isolated exceptions to this general statement may occur when patients are treated by the mushroom-graft operation described by Franceschetti.[12] Very often enucleation offers the patient relief which he demands.

An alternative conservative treatment may be offered the patient by conjunctivoplasty. In this particular condition, the operation may be planned to cover only that area of the cornea where the edema is most intense, usually where the bullae occur. In cases where the edema is generalized and bullae are present over the entire cornea a complete conjunctival flap must be applied. In all cases the best results have occurred when the operation is combined with lamellar keratectomy, either partial or complete. In those patients subjected to a partial lamellar keratectomy, an "inlay" graft of conjunctiva and Tenon's capsule has been placed in the area of the excised cornea. There appears to be some dehydration of the adjacent corneal stroma and epithelium in these cases. In other patients, where glaucoma has coexisted with diffuse bullous keratopathy, the ocular pressure has definitely fallen after a complete lamellar keratectomy and complete permanent conjunctival covering. In these cases a large filtration area through the entire cornea is produced by the complete keratectomy. The aqueous filtering through the more permeable cornea is probably reabsorbed by the overlying conjunctiva.

*Marginal Ulcers.*—A large group of corneal diseases may be mentioned under this heading. Almost all are of unknown etiology.

A. Marginal keratitis usually occurs without ulceration but sometimes with it. Its characteristics are well known to all ophthalmologists: its acute onset and rapid development of cellular infiltration in the anterior corneal layers and sometimes the epithelium, its painfulness, its frequent association with facial rosacea, its tendency towards recurrence, and, finally, its relatively benign course and dramatic improvement after local steroid therapy. These patients rarely require surgical treatment of any sort.

B. Marginal furrows, though much rarer, are more serious. This corneal disease is sometimes called Fuch's marginal furrow, furrow dystrophy, or Terrien's dystrophy. It can occur in young adults as well as in elderly persons. There is no doubt in my mind that excess local steroid therapy has a deleterious effect on these corneas and has led to perforation in several cases. Conjunctival flaps are useful, though they need not be total or complete. Inlaid full-thickness corneal grafts have also proved to be of great value.

C. Mooren's ulcer, an eponymic corneal disease, remains poorly understood and

poorly classified, though it usually refers to to chronic granulomatous marginal keratitis with or without loss of substance. It is generally thought that if marginal keratitis heals with or without treatment that the name of Mooren's is misapplied. Conjunctival flaps have been used in this disease, and, though the results are not brilliant, usually no harm is done by the operation.

*Painful Blind Eyes.*—Disorganized and phthisical globes, when completely blind, are usually painless and cause no trouble. A few, however, cause irritation owing to band-shaped keratopathy which frequently accompanies the condition. Many patients prefer keeping these sightless eyes than having them removed, especially when a prosthetic shell can be worn over them. When the cornea is sensitive, the shell may cause irritation. Under these conditions, a total permanent conjunctival flap, especially when combined with a complete lamellar keratectomy, renders the eye painless and capable of tolerating a prosthetic shell for cosmetic purposes. The operation has been used with success in several such patients.

*Filamentary Keratitis.*—True filamentary keratitis, excluding that seen in keratitis sicca (Sjögren's syndrome), is most commonly seen as a condition following major surgical procedures such as scleral bucklings or other extensive operations for retinal detachment. It may also be seen after cataract or glaucoma operations, occurring close to the site of incision. In general the condition is transient and short-lived. There is, however, another type of filamentary keratitis which is completely idiopathic and which, when extensive, may be completely debilitating. Relief of symptoms promptly follows flapping in such cases. After removal of the conjunctival flap in one patient, the keratitis did not recur. In two other cases the flaps have been applied permanently over marginal portions of the cornea. In severe keratitis sicca, a similar operation might also be employed, but I have usually been able to render these patients comfortable by less drastic procedures, e. g., ligation or transplantation of the canaliculi.

## Technique of Operation

The application of a complete permanent or semipermanent conjunctival flap over the cornea is an operation which must be done with meticulous care. The surgeon should have a well-trained assistant and his best surgical instruments available. It should be borne in mind that the flap must be applied perfectly the first time, since there is not enough tissue available for a second try.

The following instruments and equipment have been found to be most useful:

Scissors: both straight and curved, sharp-pointed iris scissors of the best make.

Needles: Kalt corneal needles.

Sutures: finest twisted silk, finer than 000000, if available.

Also strabismus hooks, speculum with guard, needle-holder, electric or hand-cautery, and fine tissue forceps, both toothed and smooth.

Anesthesia may be either general or local, depending on the patient's age and other factors. Local procaine anesthesia is satisfactory. After preparation of the eye as for any major procedure, 2% procaine is injected into the orbicularis (Van Lint) and into the orbital apex, with use of a 5 cm. 25-gauge needle, after the technique of Gifford.[13] Complete anesthesia and akinesia of the lids and globe, save for the superior oblique muscle, follows in three to five minutes. A traction suture of silk is placed through the upper corneal limbus from 11:30 to 12:30 o'clock to control the globe and to draw it strongly downward. Thus, the entire upper bulbar conjunctiva is exposed. The distance between the upper limbus and the upper fornix varies from 16 to 18 mm. and affords an adequate covering when transposed to cover the 12 mm. cornea (Fig. 1.).

One to two cubic centimeters of 2% procaine with epinephrine 1:50,000 is then injected under the superior bulbar con-

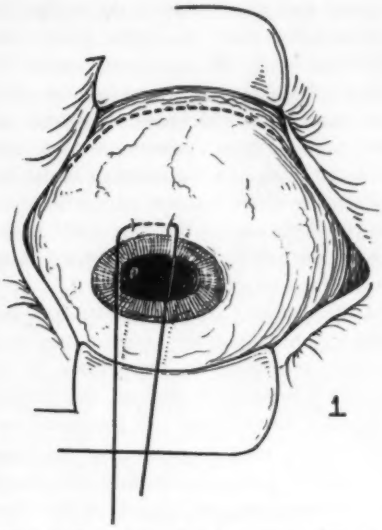


Fig. 1.—Exposure of entire upper bulbar conjunctiva by means of a traction suture placed through the upper corneal limbus.

junctiva, taking care that the injection is made through the conjunctiva near the lateral rectus. Great care must be exercised not to perforate that portion of the conjunctiva which eventually will cover the cornea. A minute hole through this portion of the conjunctiva inadvertently made with scissors, the sharp tooth of a forceps, or even a 25-gauge needle will subsequently enlarge and frequently defeat the purpose of the operation. With the conjunctiva thus ballooned up and rendered relatively ischemic by the injection, a horizontal incision is made with scissors through conjunctiva, following the reflection of the bulbar conjunctiva on the retrotarsal fold. The incision should be at least 3 cm. long, and great care should be exercised to avoid cutting the underlying Tenon capsule (Fig. 2).

The dissection of the conjunctival bridge is thus begun from the fornix and carried down to the upper limbus. Only in this way can conjunctiva be separated from Tenon's capsule and a thin flap be made. The insertions of Tenon's capsule into the overlying conjunctiva from underneath make any other dissection of such a bridge flap impossible. The dissection is greatly facilitated by an able assistant, who, with two forceps, can hold the upper edge of conjunctiva steadily forward and vary its position slightly so that the surgeon can see both surfaces of the

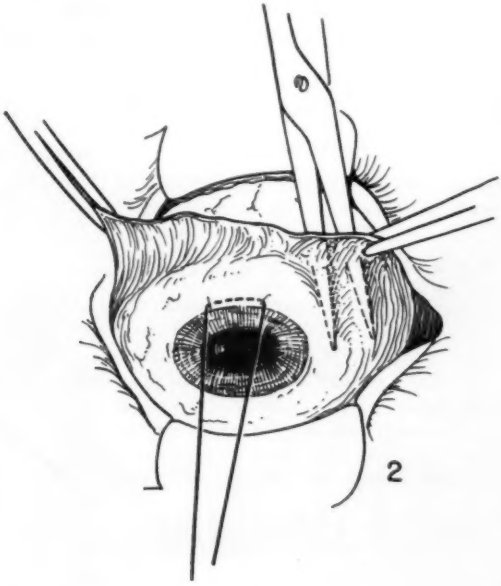


Fig. 2.—Incision through conjunctiva.

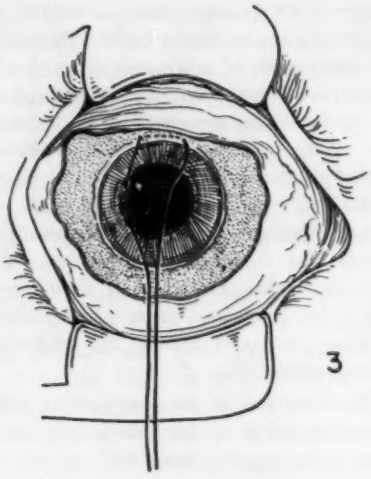


Fig. 3.—Completion of peritomy.

conjunctiva while he cuts the delicate bands between these two structures without perforating the paper-thin conjunctiva. When the limbus is reached, the conjunctiva is severed from it by scissors or cataract knife. I prefer the latter. The peritomy started above is then completed (Fig. 3). Attention is next directed toward the temporal and nasal sides of the bridge flap. If it is lifted from the globe gently on a strabismus hook, its attachments can be visualized. It is usually necessary to divide some bands and attachments between conjunctiva and Tenon's capsule, so as to allow this large bridge of conjunctiva to lie over the cornea with no traction on it whatsoever. The blood supply to the flap itself is only slightly disturbed, since the broad lateral bases remain intact (Fig. 4).

At this point, after the flap has been completely prepared, the surgeon may apply whatever treatment to the cornea he has planned: Chemical or thermal cauterization or lamellar keratectomy are the usual ones.

The flap is finally spread over the cornea and sewed in position with fine silk sutures. Two mattress sutures, placed in the superficial sclera 2 mm. from the bared limbus at 5 and 7 o'clock (Fig. 4), are brought up through the lower border of the bridge, namely, that which formerly lay over the limbus at 11 and 1 o'clock (Fig. 5). The original conjunctiva of the lower limbus, which has retracted slightly because of the peritomy, is then sewed to the lower border of the

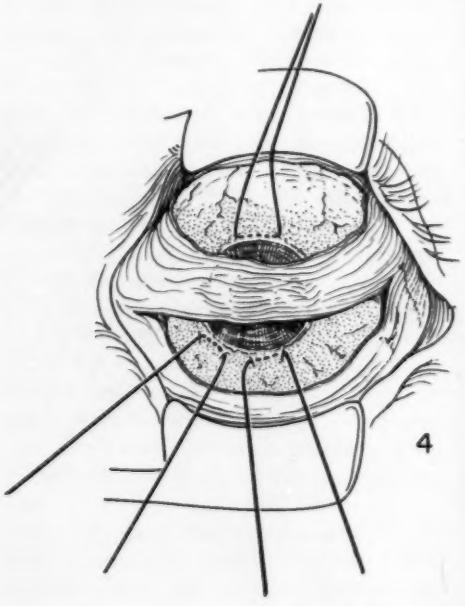


Fig. 4.—Large bridge of conjunctiva lying over the cornea.

bridge on either side of the two mattress sutures. Usually one suture on either side will suffice. The upper border of the bridge is then lying at or just above the upper limbus, and the lower edge of Tenon's capsule can be identified as a definite white slightly thickened ridge of tissue. This should be sewed to the upper border of the conjunctival bridge with five or six fine interrupted black silk sutures (Fig. 6).

Thus, the operation is complete. The entire upper globe is bare of conjunctiva, and one might have cause to fear granulations, adhesions, ptosis, and other complications. None have occurred. Epithelium appears to grow and cover the exposed Tenon capsule with astonishing rapidity.

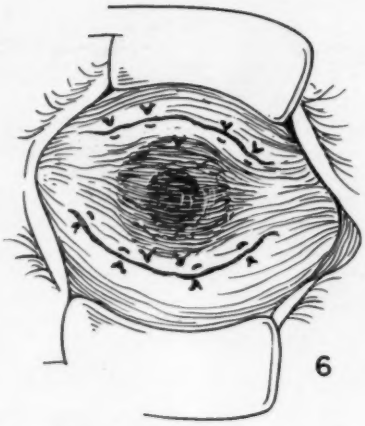


Fig. 6.—Tenon's capsule sewn to the upper border of the conjunctival bridge.

## Personal Experiences

During the past five years, I have applied 31 total permanent or semipermanent conjunctival flaps over diseased corneas. The operation has been done 21 times for patients with severe herpetic infections of the cornea, 4 times for patients with bullous keratopathy, 3 times for patients with painful blind eyes, and 1 time each for patients with filamentary keratitis, traumatic relapsing keratitis, and neuroparalytic keratitis. In one patient with severe stromal herpes, the cornea perforated under the flap, and the eye was later removed because of intractable secondary glaucoma. In all others, the flap was beneficial.

Fig. 5.—Flap spread over cornea and sewn in position.

## Summary

The use of conjunctival flaps in corneal disease is reviewed. A new technique of applying them is described whereby such a covering can be applied with complete expectation of its remaining in place as long as desired.

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# Indications for Clinical Electroretinography

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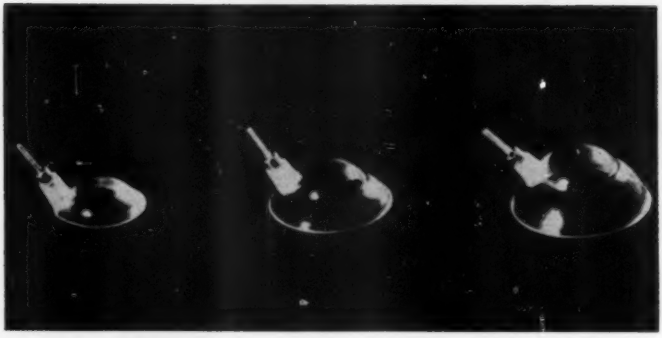

Fig. 1. — The active electrode. Three different sizes of contact glass with chlorinated silver rods.

An electric potential is produced in the retina of the eye, which makes the front of the retina and the cornea electrically positive and the back of the retina and the bulb negative. When the retina is stimulated by light this potential increases, and an electric action potential, the electroretinogram, or ERG, develops. The appearance of the curve formed by these potentials differs in various animal species and also varies with the intensity of light stimulus, as well as with the dark and light adaptation of the retina.

For clinical purposes, the potential is led off from an active electrode, consisting of a chlorinated silver rod inserted in a contact glass of plastic or glass, as first used by Riggs (1941). Contact is established between the corneal surface of the eye and the electrode by means of saline, which fills the space between contact glass and

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Fig. 2. — The intensity of the stimulus light is regulated. Standard intensities are 20, 80, and 800 lux.

Fig. 3.—After five minutes in darkness, the patient is now ready for the ERG examination in a standardized subtotal state of dark-adaptation.

cornea. The reference electrode, which is grounded, is placed elsewhere on the body. We use a reference electrode on the inside of the head band attached to the forehead. Under these conditions, a monopolar recording is obtained of the electric potentials picked up from the surface of the cornea.[15-18]

The recording is made with several steps in the intensity of stimulating light, for example, 20, 80, and 800 lux. A flash is given every 15 seconds.

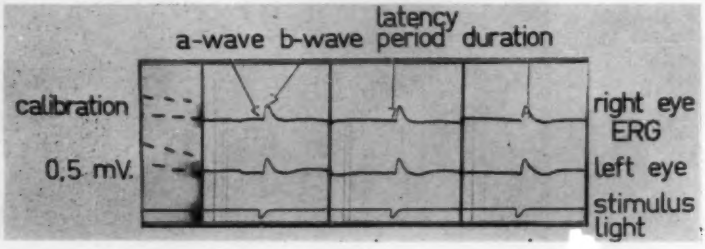
Since the ERG curve alters with a change in adaptation of the retina, it is necessary to standardize the adaptation state for clinical use. In the method applied at our clinic, a standardized semi-dark-adapted state is used. This is because complete dark adaptation for one-half hour implies great practical difficulties. Under these conditions, the light-sensitized retina is stimulated not only by direct illumination of the image of the light source on the retina but also by the scattered light, which stimulates the whole retina. Therefore, a recording cannot be made from a small pathologic area of the retina only. One always obtains an electroretinogram from the whole retina.

The clinical ERG, as I shall now present it, represents the electric response of the retina under standardized conditions of dark adaptation to single-flash stimulation.

A normal ERG consists of a small negative deflexion, the a-wave, and a large positive b-wave. In pathologic conditions, the following four types of ERG can be seen: (1) subnormal; (2) negative, of which two types are found: negative+ and negative−; (3) extinguished; (4) supernormal.

An ERG recording takes about one hour for an experienced assistant. As in many other diagnostic methods using complicated apparatus, such as determination of the

Fig. 4.—Normal ERG's of both eyes. The a-wave is not always present. The b-wave has a potential of about 0.2 to 0.5 mv. With a stimulus light of 20 lux, the latency period is 0.04 to 0.05 second and the duration, 0.15 to 0.16 second.



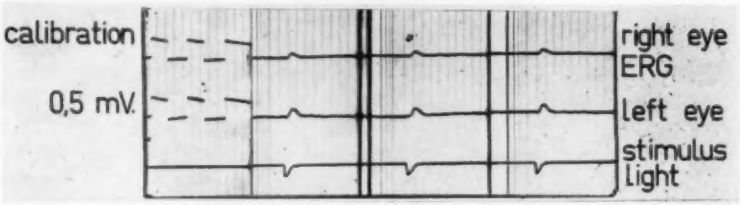



Fig. 5.—Subnormal ERG (right eye) in an eye with detachment of the retina. Normal ERG in the left eye (normal retina). A subnormal ERG is also seen when large areas of the retina do not function for some other reason, e. g., after healing of a retinal embolism, in disseminated choroiditis, or in severe myopia.

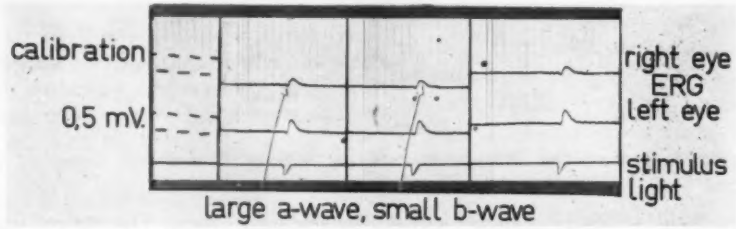



Fig. 6.—Negative ERG (right eye) in an eye with embolism of the central retinal artery. Normal ERG in the left eye. A negative ERG is seen in acute disturbances of the retinal circulation, embolism of the retinal artery, or thrombosis of the retinal veins, as well as in siderosis of the retina.

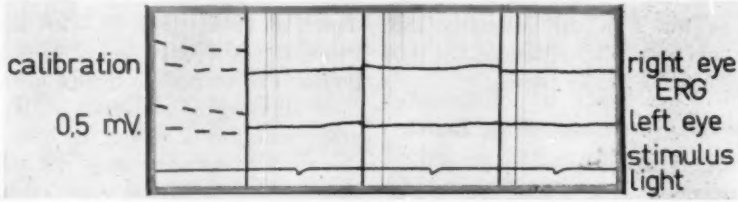



Fig. 7.—Extinguished ERG's in a case of advanced diabetes retinitis with detachment of the retina of both eyes. No ERG response even to the strongest stimulus light when retinal function fails. In primary retinitis pigmentosa the ERG is extinguished from the beginning, even from birth.

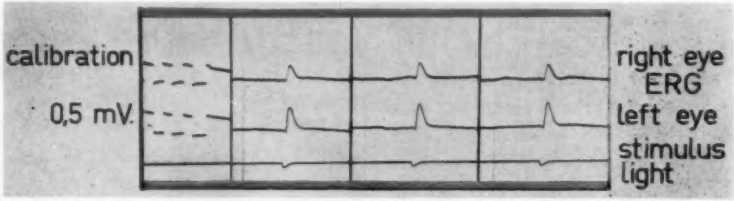



Fig. 8.—Supernormal ERG (left eye). Normal ERG in the right eye. This type of ERG is seen as the initial symptom in siderosis of the retina and in subtotal occlusion of the central retinal vein.

basal metabolism, electrocardiography, and electroencephalography, it is essential for the examination to be carried out by specially trained personnel. Otherwise, it is apt to be misleading and the results, inconclusive.

The method that I have just described has been used at the eye clinic of Karolin-

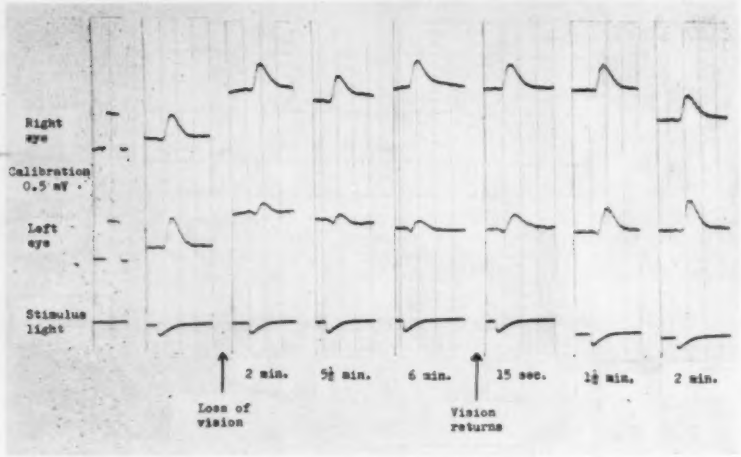



Fig. 9.—Reproduced from Nilsson, Rendahl, and Strömberg,[29] *American Journal of Ophthalmology*.

ska Sjukhuset as a routine clinical method since 1946. By now, we have made about 3500 such examinations.

I shall now present the types of eye lesions in which the ERG gives valuable information for both the diagnosis and prognosis and in which indications for this examination are therefore present.

### Circulatory Disturbances of the Retina

In circulatory disturbances of the retina, such as embolism of a retinal artery and thrombosis or strangulation of a retinal vein, great changes appear in the ERG. If only a small vessel branch is involved, the pathologic area is, however, so small that the large area of normal retina dominates the ERG, so that it often remains normal. The recording is therefore of less importance in an arterial branch embolism or in thrombosis of a branch of a retinal vein. In spasm of the central retinal artery, there is a transient change in the ERG accompanying the impairment of vision. If the spasm is transient and vision is restored, the ERG returns to normal. If it persists, or is caused by an embolus, the change in the ERG also persists. I can show the following case as an example.[11-13,22]

This is a case of transient unilateral spasm of the central retinal artery, due to polycythemia vera. The patient was a 48-year-old woman. She had repeated attacks of loss of vision for two to six minutes, with narrowing of the arteries of the fundus.[29,30] It was possible to record the ERG during an attack (Fig. 9). This shows that strangulation of the central retinal artery produces an immediate change in the ERG.

In all cases of embolism of the central artery with loss of vision, the ERG is negative (—) in the acute stage and later often becomes subnormal or even extinguished.

In central vein thrombosis, all the types of ERG might appear. In those cases in which the b-potential is greatly decreased, the prognosis is consistently poor. The vis-

TABLE 1.—*Thrombosis of the Central Retinal Vein*

| b-Potential and Prognosis | | Cases, No. | V.A. After Healing |
|---|---|---|---|
| b-Pot. big, good prognosis | supernormal ERG | 3 | 20/30 |
| | neg. + ERG | 2 | |
| | normal ERG | 12 | |
| | | 17 | |
| b-Pot. big, bad prognosis | normal ERG | 12 | 20/250 |
| b-Pot. small, bad prognosis | neg. — ERG | 25 | 20/220 |
| | subnormal ERG | 16 | |
| | extinguished ERG | 3 | |
| | | 44 | |
| | Total No. of cases | 73 | |

ual acuity is generally less than 20/200. If the retinal damage is not as severe, the ERG may remain normal or become supernormal. The prognosis may then be more favorable, as shown in Table 1. In these cases, the average visual acuity after healing is 20/30.

Thus, in central vein thrombosis not only does the ERG provide diagnostic information but it also throws light on the prognosis and the probable function after healing.

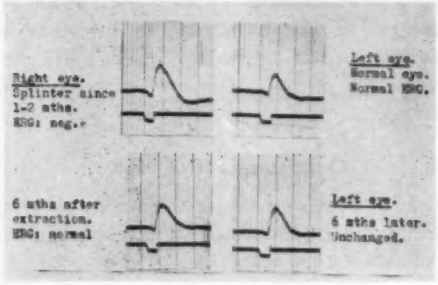
When the ERG is normal or supernormal, I consider that there are indications for long-term bishydroxycoumarin (Dicumarol) or heparin therapy to prevent further development of the thrombus with a detrimental effect on the retina.

### Metallosis—Siderosis

Symptoms of siderosis were present in 21 of 41 patients with a metal splinter in the eye for more than two weeks. Three of them had an ERG of negative+ type; nine, of negative− type, and another nine, an extinguished ERG. The remainder had no clinical signs of siderosis and a normal ERG, owing to either the fact that the splinter was of stainless steel or that it had not been sufficiently long in the eye.[16-18,20,28]

STAGE 1.—ERG negative+. The following patient is an example of Stage 1, in which the ERG is negative+. He was struck in the eye by a metal splinter while chiseling. Impairment of vision developed one to two months later. The diagnosis of siderosis was at first uncertain clinically, since the visual fields were normal and the dark-adapted threshold was also normal. Except for a fine aqueous flare, there were no pathologic changes. However, the ERG was negative+. Note the increased a- and b-wave. The splinter was then detected on x-ray examination and extracted. Six months later the ERG had become normalized and vision was normal.

Fig. 10.—ERG in a case of siderosis, Stage 1.



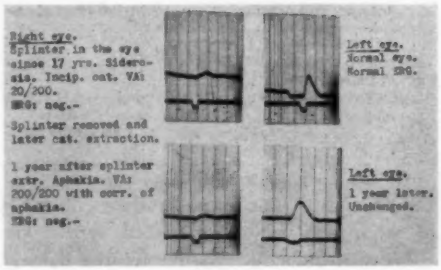




Fig. 11.—ERG in a case of siderosis, Stage 2.

STAGE 2.—ERG negative−. All these nine patients had clinical signs of siderosis. Some of them had pigmentation of the iris, and others had an increased dark-adapted threshold or contracted visual fields. The case in Figure 11 is an example of this type.

STAGE 3.—ERG extinguished. All the cases with an extinguished ERG have atrophy and pigmentation of the iris, an increased dark-adapted threshold, and contracted visual fields.

Sometimes, although a metal splinter is present in the bulb, there are reasons to believe that metallosis is not bound to develop. For instance, the splinter may be of stainless material or it may be incapsulated in the wall, without any direct contact with the intraocular fluid. In such cases it is often wiser to refrain from extraction, which is a risky operation. We then use the ERG as a routine follow-up method, to check whether or not metallosis of the retina has started to develop. If a pathologic ERG is recorded, this is an indication for extraction of the splinter, even if it is nonmagnetic or is not easily accessible.

### Detachment of the Retina

Rendahl has studied the ERG in 250 cases of detachment of the retina.[16-18,21,24]

TABLE 2.—*Detachment of the Retina*

| | | | |
|---|---|---|---|
| Total No. of cases examined: 250 | | | |
| Cases operated on: 144 | | | |
| Healed after op. | 74 | — b-Pot. before op. | 0.14 mv. |
| Not healed after op. | 70 | — b-Pot. before op. | 0.09 mv. |
| | | Difference | 0.05±0.015 mv. |

Detachment of the retina produces an ERG of subnormal or extinguished type. The ERG also indicates how severe the damage is. If the b-potential is greatly reduced in size, there is severe retinal damage and the prospects of reattachment after operation are poor (Table 2).

Jacobson and co-workers (1958) confirmed, in a series of 50 cases of retinal detachment, that the ERG can give prognostic information about the function. The larger the b-potential, the better the function after operation. I should, however, like to stress that in these cases the result of ERG examination is only one of the many factors that must be taken into consideration when one is deciding to refrain from operation in a particular case. I can show two cases as an example (Figs. 12 and 13).

At our clinic, we perform ERG in every case of detachment of the retina.

## Retinitis Pigmentosa and Other Forms of Tapetoretinal Degeneration

By now, ERG studies have been made altogether in about 100 cases of these eye diseases. In genuine retinitis pigmentosa the ERG is extinguished. This occurs even at a very early age, for example, in children

Fig. 12.—ERG. Retinal detachment in the right eye. Symptoms of six weeks' duration.

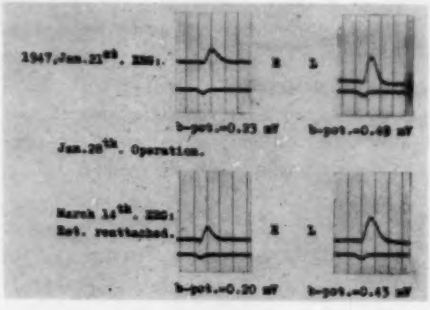


Fig. 13.—ERG. Retinal detachment in the left eye. Right eye, myopia=—18, V=0.3, conus myopic, full field, no detachment. Left eye, nearly half of retina detached since two weeks previously. ERG before operation. No reattachment.

less than one year old belonging to families in which the mode of inheritance of the disease is dominant.[2] Recording of the ERG can also be of importance if, for instance, the question arises of sterilizing the parent who is the carrier of the hereditary trait. In nongenuine retinitis pigmentosa, in which, however, the typical fundus changes are present as well as suspected limitation of the visual fields, the ERG is, on the contrary, subnormal unless the disease is very advanced. Such cases, which have been denoted as secondary retinitis pigmentosa, are generally caused by retinitis or vascular lesions of the retina.

Another closely related retinal disorder is retinitis punctata albescens. In the benign and stationary form the ERG is normal, whereas in the malignant, progressive form it is subnormal or extinguished.[4-6] Both a normal and a pathologic ERG may be seen in other similar retinal diseases, such as amaurotic family idiocy (Tay-Sachs' disease), gyrate atrophy of the choroid, choroideremia, heredoretinopathia congenitalis,[1] and hereditary ataxia with retinal degeneration.[3]

## Avitaminosis A

An extinguished ERG is occasionally seen in avitaminosis A when the vitamin A content of the blood has fallen below a certain borderline value.[7] The ERG returns to normal after administration of large quantities of vitamin A.

## Opacities of the Media

In opacities of the media which prevent inspection of the fundi, it is important in certain cases to obtain an objective record-

TABLE 3.—*Opacities of the Media*

| | Before Cat. Op. | After Cat. Op. | Difference |
|---|---|---|---|
| b-Pot., mv. | 0.30 | 0.28 | 0.02±0.015 |
| Latency, sec., 20 lux | 0.05 | 0.04 | 0.01±0.003 |
| Latency, sec., 80 lux | 0.04 | 0.04 | |
| Duration, sec., 20 lux | 0.17 | 0.15 | 0.02±0.007 |
| Duration, sec., 80 lux | 0.15 | 0.14 | |

ing of the action potential of the retina with the help of the ERG. In senile cataract, the ERG is normal, and the size of the b-potential is about the same before and after extraction of the cataract.[23] Senile degeneration of the macula or central choroiditis cannot, however, be diagnosed with this type of electroretinography. The normal ERG which arises in the whole peripheral surface of the retina predominates. The ERG recorded will therefore be normal.

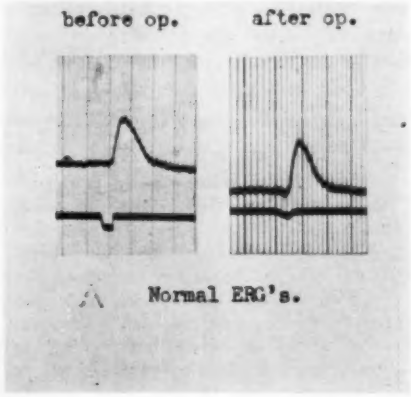
In cases of complicated cataract, for instance, chronic uveitis with cataract, extensive retinal damage can be suspected. An operation is risky, owing to the complications. A normal preoperative ERG strengthens the indications for operation. An extinguished ERG is a contraindication.

The ERG has the same importance in the presence of corneal opacities, when it is intended to make a corneal graft.

When an intraocular tumor is present, the ERG will be subnormal to the extent that the tumor has damaged the retinal veins or has produced detachment of the retina.

In glaucoma changes in the ERG are seen only when the raised intraocular tension has affected the retinal circulation.

Fig. 14.—ERG in a case of cataract.




## Retroretinal Damage

If impairment of vision is due to injury to the optic nerve, the visual paths, or the visual cortex but the retina is intact, a normal ERG will be recorded. This could be shown in one of our cases with atrophy of the optic nerve of one eye, which was amaurotic and had a china-white disc, after repeated attacks of retrobulbar neuritis caused by disseminated sclerosis. The pathologic process was confined to the optic nerve, whereas the retina was intact. The ERG of both eyes was the same, that of the blind eye and that of the other eye, which was completely normal. This shows that it is often possible to determine, on the basis of the ERG, whether a retinal or a retroretinal process is responsible for optic atrophy and loss of vision.

I have preferred to confine myself to an account of a single method for clinical recording to the ERG, namely, that in which I have experience. Electroretinography is, however, a relatively new method of examination, which is still in the course of development, and several other techniques for recording exist. Among them are those of Henkes, Monnier, and Schmöger.

Many improvements can be expected in this field. In particular, it can be presumed that flicker electroretinography, which allows recording from the light-adapted retina, will give new results. It is, for instance, possible with this method to diagnose total color blindness[8] and to analyze the so-called x-potential[9] and the photopic action potential in a light-adapted eye.[10] Moreover, it has permitted two types of red blindness or protanopia to be distinguished,[10] as well as two types of green blindness or deuteranopia.[25] Since this method is still in the very early stages of development and

has not yet been used to any great extent for clinical purposes, I shall not enter into any details of it.

Karolinska Sjukhuset.

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# The Treatment of Retinoblastoma by X-Ray and Triethylene Melamine

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We have been treating retinoblastoma by irradiation according to the method described by us first in 1936.[1] The technique, which was devised by Dr. Hayes E. Martin, of the Memorial Center for Cancer and Allied Diseases, includes the employment of special cones and a temporal and nasal port in an effort to deliver an adequate dose to the posterior sector of the eye to the exclusion of the vulnerable anterior sector. Subsequent reports on the use of this technique were made in 1942,[2] 1945,[3] 1949,[4] 1955,[5] and 1957.[6] The treatment is employed for patients with bilateral tumors whose eye with the more advanced disease has been enucleated. The less involved eye has been treated when it was thought that useful vision might be salvaged if the tumor were arrested.

From the institution of this treatment in 1936 through 1952 we treated by this method 195 patients falling within the category stated here, i. e., one eye enucleated and the fellow eye, with less-advanced disease, treated.

The over-all cure rate with vision was 36%; 12% had very limited vision (10/200 to H. M.), leaving only 24% with useful vision. By selecting the last 22 consecutive eyes treated with x-radiation, using tumor doses ranging from 9200 r to 6500 r, the cure rate with vision was 50%. Of the 50% failures, eight required enucleation because the tumor was not under control and three had no vision, owing to vitreous hemorrhages, but the tumor was arrested. The better results in the more recent cases were due to a refinement in technique and more attention to detail. The higher percentage of patients cured with vision was due to the fact that in the earlier cases we used 10,800 r, which led to intractable complications, the most important of which was vitreous hemorrhage.

Because of these intraocular complications, which in many instances marred what seemed to be a satisfactory result, we tried to reduce the dose of x-ray to the very minimum and to treat very small lesions with diathermy.

We reduced the dose to 3000 r, with the result that fewer complications seemed to occur, and, at the same time, this dose seemed lethal to the tumor.

We were questioning whether or not our x-ray dose could be reduced even further; we had our doubts about the feasibility of treating any but the very small lesions by diathermy and some qualms regarding the degree of effectiveness of this treatment, even for the small lesion, when, by permission of Dr. Alan C. Woods, we saw a patient with advanced retinoblastoma that had shown a remarkable regression with the use of radiation in combination with nitrogen mustard therapy. This case was reported by Dr. Carl Kupfer.[7] Combining x-ray treatment with a radiomimetic drug seemed to offer a good opportunity to reduce our x-ray dose even more.

We have given, in previous publications, our reasons for selecting triethylene melamine (TEM) as our drug of choice, on the

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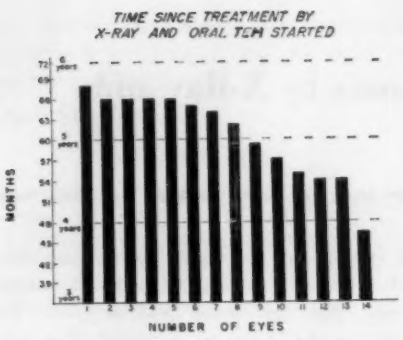



Fig. 1.—Oral triethylene melamine.

basis of experimental work as well as clinical observations. In January, 1953, we started to treat all suitable cases with a tumor dose of x-ray reduced to 3250 r in combination with TEM administered orally. In 1955 we gave a report on 20 eyes treated by this method. Of these 20, a total of 70% were cured to that date. These eyes still show complete tumor arrest, and we believe that they can be reported now as cures. There have been no vitreous hemorrhages and no sequelae to the irradiation. No cataracts have developed. Figure 1 shows the amount of time that has elapsed since treatment was started in the 14 successful cases. All of the patients have normal vision except two, in whom the lesion was directly in the macular area. These patients have better than 20/200 vision; all the others have vision ranging from 20/30 to 20/20.

We believe that the elapsed time since such treatment was started warrants considering these cases as cures, particularly in view of the fact that this tumor is in transparent media, magnified 16 times by the ophthalmoscope, and therefore it is possible for us in a reasonably short time (usually six months) to predict whether or not the tumor has been arrested. We have observed only three eyes in which we detected active growth following treatment after a longer period had elapsed. The periods were 2 years 11 months, 1 year 10 months, and 1 year 6 months, respectively. These are the longest periods that have ever elapsed between the completion of treatment and detection of active growth.*

In September, 1955, the oral form of TEM was discarded because emesis and irregularity of absorption interfered with the accuracy of the dosage, especially when leukopenia or thrombopenia did not develop.

Therefore, when a parenteral preparation of TEM became available we discarded the oral route. We have treated 19 consecutive suitable cases by the combination of 3250 r with intramuscular injection of TEM. To date 17 of the 19 (89%) appear arrested. Of the two failures, one patient could not have further TEM for four and one-half months after the first injection because of bone marrow depression. The patient then received intra-arterial TEM, and the tumor appears arrested; the other patient received intra-arterial TEM, and the tumor appears arrested. Figure 2 lists these cases with the amount of time which has elapsed since treatment was started. It is too early to claim a cure for all of these cases, but we can say that we have observed the lesions regularly at three-month intervals and they are all now in a state that we usually asso-

* In reviewing all of our patients we find one who had been treated by x-ray in May, 1944, with apparent arrest of the tumor and vision of 20/40. In July, 1953, enucleation had to be done for intractable glaucoma. Recurrent tumor in the nose and sinuses was noted in January, 1958. Another patient was treated by x-ray in April, 1938, and recurrent growth was diagnosed in September, 1944. These illustrate the very rare exceptions.

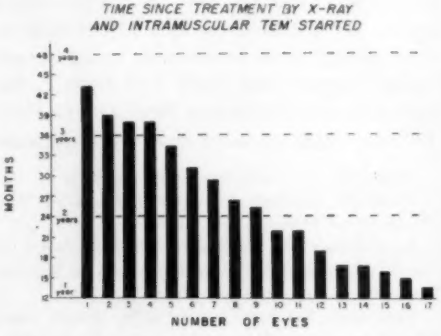



Fig. 2.—X-ray and intramuscular triethylene melamine.

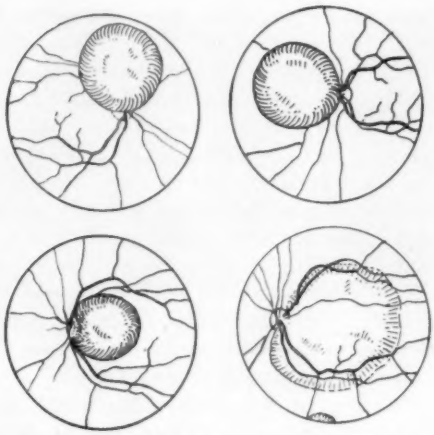


Fig. 3.—Diagrams of the tumors in four eyes considered favorable for treatment.

ciate with arrested disease. Although most of these patients are too young to record vision, there is no reason to believe that they do not have normal vision except in the exceptional case where the tumor involved the macular area.

Although the statistics and especially our recent ones on the intramuscular use of TEM, as well as our clinical impression, indicate that the combination treatment of x-ray with TEM is superior to x-ray alone, we felt that we should establish the additive virtue of TEM by running an alternate series. For this series we used favorable and as nearly comparable cases as possible (Fig. 3). To one group our routine x-ray treatment of 3250 r was given, and to the other, the same x-ray and, in addition, our routine intramuscular TEM. To date this series consists of 12 eyes: six treated with x-ray and six treated with x-ray and TEM. Three of the six eyes treated with x-ray showed active growth after the treatment was completed, and three tumors are arrested to date. The three failures were then treated with x-ray and intra-arterial TEM, and all three tumors appear arrested to date. The six eyes in the alternate series, treated with x-ray and intramuscular TEM, all appear arrested to date.

This small series indicates that the additive or synergic effect of TEM is an effective factor in the treatment. It is becoming increasingly difficult to conduct this series, because after the apparent virtue of a modality is known it cannot easily be withheld. Then, too, the statistics seem convincingly conclusive, and so our present plan is to discontinue this alternate series.

For the more desperate cases we have added the intra-arterial route of treatment with TEM. The drug is instilled under direct observation into the internal carotid artery on the side of the involved eye. The level of the chemotherapeutic agent reaching a localized tumor via the regional arterial supply can be many times greater than that given orally or intramuscularly (Klopp,[8] Sullivan[9]). On theoretical grounds regional therapy seems especially well adapted to the treatment of retinoblastoma, in view of the anatomy and blood supply of the retina.

The intra-arterial route for TEM is selected for the following groups of cases:

(1) Cases with large multiple lesions but still enough normal-appearing retina left in situ so that if tumor arrest can be accomplished there would be some useful vision

(2) Cases with tumor seeds in the vitreous

(3) Cases with intraocular lesions unsuccessfully treated by other methods—diathermy, x-ray alone, or x-ray with oral or intramuscular TEM

(4) Cases of residual tumor in the optic nerve discovered after enucleation

(5) Cases of residual tumor discovered in the orbital tissue, either in the intervaginal space or around the optic nerve, having reached these sites because of choroidal invasion, which is usually present only in the advanced lesions

(6) Cases of recurrent orbital growth after enucleation

(7) Cases that have been treated elsewhere by various combinations of treatment, including different means of employing x-ray or radon and, in some instances, diathermy, but with recurrent growth present

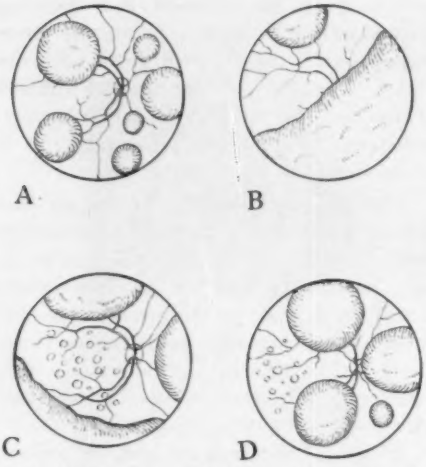



Fig. 4.—Four eyes with advanced lesions treated by x-ray and triethylene melamine intra-arterially. *a*, An eye with six foci. *b*, An eye with half the retina involved. The detached retina covers the disc. Another large solitary focus is seen. *c*, An eye with three large tumor areas. The circles indicate tumor seeds in the vitreous. *d*, An eye with four foci and tumor seeds in the vitreous.

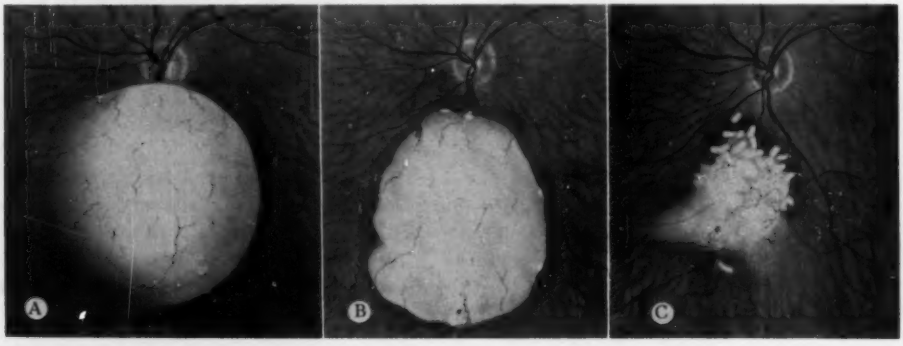
We have treated in the above categories 31 children, with a total of 61 intracarotid injections.

At the present time we wish to report only on 23 of the 31 patients belonging to groups 1, 2, and 3. These all had advanced intraocular lesions for which, in the past, enucleation would have been indicated, at least for the majority (Fig. 4). Eighteen of these had had no previous treatment, three had been failures by x-ray alone, and two had been failures by x-ray and intramuscular TEM. Fourteen of these, or 60%, appear arrested to date. The elapsed time since treatment was started ranges from over 3 years to over 6 months, so that it is not in order yet to claim cures. In view of the advanced state of the lesions, it seems to be asking too much to expect a cure rate so high. Suffice it to say now that the clinical response has been most encouraging and at present, from our regular follow-up every 6 weeks to 2 months, we have no reason to suspect active growth in these 14 eyes.

In view of the remarkable clinical response of the lesions to intra-arterial therapy, research is being done with use of carbon-14-labeled TEM in an attempt to see whether the intra-arterial route may not have a sufficient advantage over the intramuscular route to warrant using it even in the favorable case.

It is amazing to see the clinical regression of a lesion following the employment of x-ray together with one injection of TEM by way of the carotid artery. After the first two weeks little change is noted. After the third week there is a general over-all shrinkage of the tumor with perhaps a small amount of calcium, but in general the tumor is very nearly the same. Between the third and fourth weeks a truly astounding change takes place, whereby the entire mass dis-

Fig. 5.—*a*, An eye with a large tumor before treatment by x-ray and triethylene melamine intra-arterially. One small focus of calcium is present. *b*, The same case three weeks after treatment was started. The tumor has shrunk somewhat and around its periphery are atropic and pigment changes. *c*, The same case one week later or four weeks after treatment. The tumor is reduced to calcium.



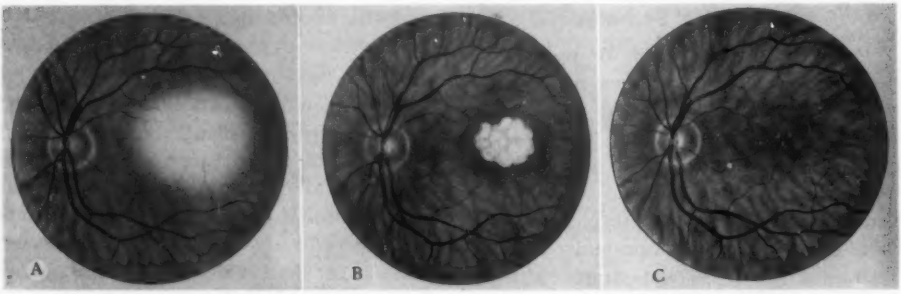
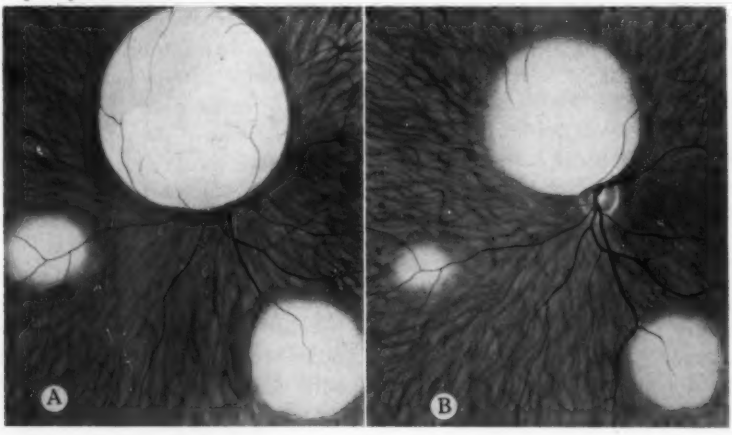



Fig. 6.—*a*, A retinoblastoma before treatment by x-ray and triethylene melamine intramuscularly. *b*, The same lesion reduced to calcium three weeks after treatment was started. *c*, The same area with calcium absorbed three months later. The only visible remains are three pinpoint flecks of calcium. The patient is too young to determine vision but from the appearance of the macula we expect it to be good.

integrates, leaving a central framework of calcium (Fig. 5). It is possible that in the future it will prove feasible to treat all cases by x-ray together with one intra-arterial injection of the chemotherapeutic agent instead of the multiple doses intramuscularly. This would be preferable, of course, to the rather long-drawn-out treatment period during which blood cell counts and repeated visits are necessary when the drug is given intramuscularly.

Following the x-ray treatment and intramuscular or intracarotid administration of TEM there are three ways by which the lesion manifests itself in the arrested stage. The commonest is that between the third and fourth weeks the tumor clinically disintegrates into calcium and the absorption of this calcium proceeds so that ultimately there may be little or no trace of the tumor (Fig. 6). Total disappearance may occur in a lesion as large as 2 to 3 D. D. in diameter. The absorption of calcium takes place over a period of about a year. Another type of tumor residium is when no calcification is manifested but the net result is seen as a grayish-white, avascular mass considerably smaller than the original (Fig. 7). Still another manifestation is a lesion the central part of which is calcified and the periphery of which is a grayish, homogeneous, avascular tissue, surrounding which is a zone of atrophy and pigment disturbance. The type of residue seen may be determined by the exophytum or endophytum character of the tumor.

Fig. 7.—*a*, Three areas of retinoblastoma before treatment by x-ray and triethylene melamine intra-arterially. *b*, Three years after treatment. The three lesions are somewhat smaller and completely avascular.



### Irradiation Technique

Positioning of the child for treatment is very important and requires patience and persistence on the part of the therapist, his assistant, and the parents of the child. The most satisfactory treatment couch has been found to be a high table on wheels which can be locked. The child is placed on the table in the supine position and is securely restrained by sheets and straps. Although with older children this may not be necessary, the age group of most of these patients is such that restraints are almost always required. It is essential that the child be kept as motionless as possible. The head is positioned so that the chin is elevated, and there must be no rotation of the head on the horizontal axis. To maintain the head in this position throughout treatment we use an evacuated fixation device which, arranged securely around the head, permits practically no motion. This device has been developed by Picker X-Ray Corporation and is known as "Flexicast." It is a thin-walled rubber bag filled with fine plastic granules which, when the bag is evacuated by means of a suction pump, form a mass, thus "fixing" the part as though in a plaster cast.

The above described fixation of the child and head permit the parent to be out of the room in the majority of cases. Previously a very satisfactory technique of fixing the child's head had been developed by having one of the parents hold the head. Obviously, although no known sequelae had developed among the parents and the calculated total-body irradiation was of a very low order, it is desirable to have the parent out of the room if the child can be held motionless by other means. In some cases it is necessary for a parent to be in the room, but his hands are kept well away from the beam and he may be able to stand away from the table.

Anesthesia or sedation for these patients is not usually feasible in that the radiation is administered daily. Most often we have been able to avoid sedation, but in several very difficult patients whose fear made them almost uncontrollable we have used methylparafynol (Dormison) or pentobarbital (Nembutal) suppositories daily.

Before the first treatment is administered, a contour of the patient's head is obtained, with careful measurements being taken in reference to distances from the port face and the orbital structures. The contour and measurements are transferred to centimeter-ruled paper, and isodose curves are applied for determination of the daily dosage to be delivered to attain the desired tumor dose throughout the retina. As might be expected, the amount of variation in the daily dosage in many of the cases is relatively little, but there are some extremes. As we are anxious not to underdose or overdose any case, we feel that careful treatment planning is indicated for each patient.

The treatment factors are as follows: 220 kv., 20 ma., target-skin distance 50 cm., filters 0.5 mm. Cu and 1 mm. Al, half-value layer 1 mm. Cu. Any type of orthovoltage equipment is satisfactory for administering this treatment. Supervoltage offers certain technical advantages, but the biologic effect is probably comparable to that of orthovoltage radiation. The tumor dose is 3500 r delivered over a three-week period.

The temporal port used in the majority of cases measures 3×4 cm., the 4 cm. diameter being in the cephalocaudad direction. A 2.5 cm. circle has been used very successfully in the past, but if one considers that the diameter of the globe is from 2 to 2.5 cm. one's beam direction would have to be consistently perfect and the patient would have to remain completely motionless not to have portions of the retina lying outside the beam on occasions. It is true that one should not enlarge the port excessively to compensate for poor beam direction or poor maintenance of the child's position. However, the multitude of variables in positioning each day and the fact that even quiet respiration moves the head several millimeters make it apparent that having a leeway of only 2 to 3 mm. is unsatisfactory. The temporal port is applied so that the mid-

portion of the anterior edge of the port is on a line with the palpebral fissure. The anterior margin of the beam is at the level of the limbus and the lateral orbital rim, these anterior limits permitting passage of the beam posterior to the lens. The beam is angled 5 degrees off the horizontal toward the floor to compensate for the divergence of the beam.

The nasal portal, which may measure 2 or 2.5 cm. in diameter, the smaller size most often being used, has a rounded methacrylate (Lucite) tip which can be positioned firmly against the bridge of the nose in the anophthalmic orbit. A curved flange mounted on the barrel of the portal passes over the bridge of the nose and rests against the lid of the eye to be treated. The tip of this flange is parallel with the treatment beam. The flange is helpful in determining the direction of the beam and, therefore, the degree of angulation required for passage of the beam posterior to the lens. This angulation is found to vary between 24 and 30 degrees. Localization films with a contact lens with markers in place are obtained, with utilization of the double-exposure technique, and are of assistance in determining the structures included in the treatment beam. Careful setting up of the patient and positioning of the portals daily is essential in the treatment of these patients. We treat one portal daily, alternating between the temporal and nasal cones each day.

With careful application of the treatment beams inadvertent irradiation of the anterior structures of the eye should not occur. The early reactions observed will be in association with the skin and the anophthalmic orbit. The acute skin reaction is a follicular erythema which develops towards the end of treatment and reaches its height at one to two weeks after treatment. This is followed by a dry desquamation. On occasion a moist desquamation may occur, which is best treated by simple cleansing and application of sterile petrolatum jelly (Vaseline). With the lowered dose of radiation being delivered we do not expect severe late irradiation changes to occur, and up to the present time we have seen no unusual sequelae. One might expect minimal atrophy and telangiectasis of the treated skin in some patients. Atrophy and underdevelopment of the subcutaneous tissues including the bone should not occur, except in isolated patients peculiarly sensitive to radiation, with this lowered dose of x-ray.

### TEM Technique

The oral administration of TEM led to both vomiting and irregularity of absorption, which made it difficult to assay properly the dose of the drug given. This was brought out strikingly by the frequent failure of hemopoietic depression to occur, which, in turn, is the most valuable index of adequate TEM therapy. When an intramuscular preparation of TEM became available (Lederle Laboratories), it was found that this drug gave reproducible therapeutic results which could be quantitated by reproducible hematologic depressions. Thus chemotherapy could be based on a pharmacologic dose-weight relationship in the individual patient.

In the 31 children each with two intracarotid instillations of TEM we have encountered only one immediate toxic effect, that of an epileptic seizure in one child at 4 and 24 hours after administration of TEM, which was not associated with any later sequelae. The systemic effects are exactly similar to those with intramuscular TEM, with immediate nausea and vomiting, as well as occasional fever for 24 to 48 hours in the smaller children. These are controllable, if necessary, by the use of chlorpromazine (Thorazine). The later hematologic effects are exactly similar to those with intramuscular TEM, with a maximum depression of white cell count reached generally on the 6th day and the maximum platelet depression reached on the 23d day after therapy. The necessity for careful care and the importance of proper dosage of TEM in the management of these youngsters cannot be overemphasized.

A most important aspect of this combination therapy of TEM with x-ray is the toxicity of this chemotherapeutic agent. Since we started its use in 1953 there has been only 1 death attributable to hematologic depression in our group of about 100 children treated. This occurred in a child receiving oral therapy, early in our experience, who suffered a subdural hematoma while thrombopenic. It is necessary to emphasize again the extreme caution that therapy with TEM requires. Because of the occasional unpredictable individual sensitivity to TEM, we have reduced the recommended dose from 0.1 mg. per kilogram of body weight in the initial course to 0.08 mg. per kilogram of body weight initially, when the drug is given intramuscularly or intra-arterially. The additional doses required can be estimated by the depth of first and subsequent hematologic depressions in the individual case and the duration of the depression. We generally treat our cases with an initial dose of 0.08 mg. per kilogram, given intramuscularly or intra-arterially, and followed on the next day with x-rays. Soon after the x-ray course is completed, and when the hemogram has returned to normal, a second dose is administered. When the drug is administered intramuscularly, a third and a fourth dose may be required several months apart, again after the hemogram has returned to normal, when the child returns for examination. We have never given more than two doses intra-arterially. In very small children or in children under 6 months of age the initial dose may be further reduced to approximately 0.06 mg. per kilogram.

Although in no instance have we had any fatality during the parenteral use of TEM, the Table will serve to substantiate the reasons for care in the selection of a proper dosage for the individual case. We feel that a maximal depression to approximately 3000 leukocytes and/or a maximal depression of approximately 100,000 platelets indicates that the patient has received an adequate dose of TEM. In the group of

*Intra-Arterial Triethylene Melamine in Combination with X-Rays*

| Hematologic Depression (0.1 Mg. per Kg.) * | | | | | | |
|---|---|---|---|---|---|---|
| | Maximal Depression of Leukocytes | | | Maximal Depression of Platelets | | |
| Cases, No. | >3000 | <3000 | Cases, No. | >150,000 | 100,000 to 150,000 | <100,000 |
| 36 | 18 | 18 | 21 | 2 | 12 | 7 |

* Former dosage used. Presently recommended initial dosage is 0.08 mg/kg. All patients had some degree of leukopenia.

patients receiving 0.1 mg. per kilogram, 50% of the youngsters had white cell counts below 3000, ranging from approximately 1400 to 3000. In addition, 33% of the children had platelet counts below 100,000 and in one case a platelet count of 25,000 was reached. We aim to achieve a white cell count of 3000 and a platelet count of 100,000. However, in none of these instances were there clinical findings of either infection due to leukopenia or hemorrhage due to thrombopenia.

Our established routine is to treat any child whose white blood cell count drops below 2000 (with a tetracycline derivative) and to treat any child whose platelet drops below 100,000 (with prednisone [Meticorten] in doses of 2.5 mg., four times daily). This therapy is continued until the white cell count rises above 3000 and the platelet count rises above 100,000. Since no therapeutic results can be expected unless hematologic depression occurs and since hematologic depression is a measure of therapeutic effect, it can easily be seen how narrow is the margin during the use of TEM therapy in combination with x-rays in these very young patients. On the other hand, we know from experience with oral TEM that inadequate doses resulting in no hematologic depressions may lead to a greater percentage of treatment failures. Thus, the utmost caution must be observed in treating these children initially, allowing the blood cell counts to return to normal and estimating the proper subsequent doses of TEM required.

It is possible that, just as modification of x-ray therapy with dosage and different types of therapy units may achieve further improvement in our over-all cure rate of the advanced case, so, too, we may achieve further benefit with better chemotherapeutic compounds which cancer research laboratories may supply in the future.

The technique of the intracarotid injection, as done by Dr. Carl R. Feind, is carried out as follows:

An approximate 4 cm. incision is made in Langers lines just below the parotid which is usually a couple of centimeters below the mastoid process and slightly below the angle of the jaw. This incision is deepened to the sternocleidomastoid muscle which is then separated along its posterior edge from the upper posterior triangular fat. In this position we are high enough to avoid the spinal accessory nerve which is still within the substance of the sternocleidomastoid muscle before it traverses the posterior triangle. This incision is deepened to the carotid sheath, where the internal jugular vein, the vagus nerve, the posterior belly of the diegastric muscle, and the hypoglossal nerve are identified. All these structures are retracted anteriorly so the internal carotid artery and the carotid bulb are exposed. We have not found it necessary to inject procaine into the carotid bulb at this point in the procedure. The entire circumference of the internal carotid artery is freed and a suture ligature of heavy silk is placed around it for traction and to steady the vessel during the injection. We have found in a small percentage of cases a very tiny internal carotid artery which makes canalization of it very difficult even with a No. 26 needle. We prefer to use a short hockey stick needle, as this gives better stability and maneuverability when injecting the drug. In some children in whom the internal carotid artery is too small for injection we free the external carotid and place a ligature around it: upon traction its flow is occluded. While the flow is occluded we inject the TEM over a two-minute period. The dosage schedule is on the basis of body weight as previously mentioned, and the drug is diluted to 1 mg. per cubic centimeter. In almost all cases we are able to inject the drug directly; this is done by pulling up on the traction suture on the proximal aspect of the internal carotid artery while the drug is injected distally over a two-minute period. One must be sure that the needle is within the lumen, as the drug in the concentration used is rather toxic to tissues. Upon completion of the injection a small peanut sponge is placed with slight pressure over the opening for a few minutes, and this usually is sufficient to stop any leakage from the puncture wound.

When a second injection is given to the same carotid artery the first scar is excised. The natural planes are involved with scar tissue from the previous procedure and this necessitates a slightly slower and more tedious dissection to prevent injury to the vital structures named above which may be masked in the scar tissue. Once the area of the artery is reached very little adherence of the scar tissue to the adventitia of the artery itself is found: the injection is usually done without difficulty.

## Follow-Up

All patients treated are examined under general anesthesia every two to four months over a period of years. We are using Fluothane now instead of chloroform and find it most satisfactory.

## Summary

We are reporting here approximately a 90% cure to date with a combination treatment employing triethylene melamine (TEM) intramuscularly with x-ray. It is our firm conviction that this is not too high a cure rate to expect. Our series using TEM orally with a 70% cure rate was reported at about a comparable post-treatment period and not one has shown recurrent growth.

The advanced intraocular lesions for which in the past enucleation would have been advised show arrested growth to date

in 60% of the cases with administration of TEM by way of the carotid artery. It is too early and no doubt too optimistic to claim or expect a cure in all of these.

Radiation alone may cure retinoblastoma but, so far as we know, TEM alone does not. The two seem to be synergistic or supplementary. That the addition of TEM is effective is evidenced by the fact that in a series of 12 cases with alternate treatment between x-ray and x-ray plus TEM three of the six eyes treated by x-ray alone showed active growth while all of those treated by x-ray plus TEM are arrested.

We surmise that in the future in the interest of salvaging more cases more effectively and in a shorter treatment time, we shall be using betatron therapy (it has been employed in our more recent cases) in combination with intra-arterial TEM or some better drug. It is now possible to label the carbon in TEM,† and we are now ready to initiate experiments which we hope will show that the intra-arterial route delivers more drug to the tumor than when given otherwise.

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† Lederle Laboratories Division, American Cyanamid Company.

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# Epithelial Invasion of the Anterior Chamber

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For more than a century ophthalmologists have been interested in the growth of epithelium within the anterior chamber. Reports of this condition were published as early as 1832, when MacKenzie described a semitransparent cyst growing in the anterior chamber after a perforating injury, but it was not until 1872 that Rothmund presented the first comprehensive clinical study of epithelial cysts in the iris and anterior chamber.[1,2] Although most of his 37 cases followed injury, 2 occurred after cataract extractions, and from his investigations Rothmund concluded these cysts were caused by implantation of epithelium in the anterior chamber at the time of injury or operation. This idea was opposed by von Wecker, who thought the cysts arose spontaneously when the iris surface became infolded or adherent over a crypt, but the experiments of Masse and others and the histopathologic studies of Collins and Cross, Guaita, and Meller soon confirmed Rothmund's theory.[3-9] Since then, our knowledge has greatly increased, and in 1937 Perera was able to differentiate three types of epithelial growth within the anterior chamber: (1) "pearl" tumors of the iris, (2) post-traumatic cysts of the iris, and (3) epithelization of the anterior chamber.[10] In discussing this topic Calhoun, Duke-Elder, and Maumenee and Shannon have followed Perera's classification.[11-13]

The problem of "pearl" tumors will not be considered in this paper, for their origin is well established and Sitchevska and Payne have recently reviewed the subject.[14] Terry, Chisholm, and Schonberg and Theobald and Haas have presented the clinical and pathologic evidence leading to our present understanding of epithelial invasion of the anterior chamber and have summarized the ways in which this invasion may occur as follows: (1) implantation of free conjunctiva or cornea, (2) inturning of a conjunctival flap, and (3) epithelial ingrowth along a gaping intraocular wound, incarcerated tissue (lens capsule, vitreous, or uveal tissue), or a deeply inserted suture.[15,16] In the experiments to be described attempts were made to produce epithelization of the anterior chamber and iris or anterior chamber cysts by these methods and the factors contributing to the growth of corneal and conjunctival epithelium within the anterior chamber were studied. Before these experiments are described, the reports of previous investigators must be summarized, for the techniques used are neither new nor novel.

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## Review of Earlier Experimental Studies

*A. Implantation of Free Conjunctiva or Cornea.*—The first experimental attempts to grow epithelium in the eye were made by Dooremaal, Goldzieher, and Schweninger, who implanted various kinds of tissue, including pieces of skin, buccal mucosa, cornea, and conjunctiva, in the eyes of rabbits and dogs.[5,17,18] Although "pearl" tumors were seen, neither "post-traumatic" cysts nor epithelization of the anterior chamber was described. The earliest report of the experimental growth of a "post-traumatic cyst of the iris" is that of Masse (1880-1881), who excised a small piece of conjunctiva from each eye of 15 rabbits and immediately placed it in the anterior cham-

ber of the same eye through a linear corneal incision.[4,19-21] He found that the graft became adherent to the anterior surface of the iris, resorbed slowly, and was replaced by a translucent iris cyst. In some instances the conjunctival graft produced both an "epithelial tumor" and a cyst. Masse did not describe the development or the histology of these lesions, and no illustrations of his findings were published.

In 1885 Hosch, after implanting the superficial layers of the cornea into nine rabbit eyes, found that the corneal epithelium usually disappeared and the remaining tissue became encapsulated.[6] In six eyes small pieces of bulbar conjunctiva were placed on the iris, and in two of the six the conjunctival implant was completely absorbed while in the other four there was formed a tumor mass composed of a core of connective tissue covered by cylindrical epithelium. Hosch believed that solid, noncystic growths were formed because the implanted bulbar conjunctiva contained few or no goblet cells whose products could cause retention cysts. In three of four rabbit eyes in which skin was laid on the iris large cysts composed of pavement epithelium filled with atheromatous contents were formed.

After Hosch's work few experimental studies were made until clinical interest focused on the problem of epithelization of the anterior chamber following cataract extraction. In 1930 Suzuki reported a cystlike structure in 3 of 19 rabbit eyes after free pieces of conjunctiva were placed in the anterior chamber.[22] When conjunctival epithelium alone was inserted into the anterior chamber, no growth occurred and the epithelium disappeared.

Both Accardi and Rossi and Gundersen planted free pieces of cornea, including epithelium, within the eye.[23,24] The former investigators found that not only cornea but many other tissues, when inserted into the rabbit anterior chambers, were replaced by new-formed connective tissue. Gundersen, working with cats and rabbits, showed that the implanted cornea usually "became adherent to the iris, from which blood vessels soon entered the foreign tissue." In one instance the corneal disc remained freely movable in the anterior chamber of a cat eye. Gundersen made a histologic study of this eye 20 months after operation and reported that the epithelium had disappeared but the corneal stroma was relatively intact and endothelium had proliferated to surround the corneal disc. From his experimental studies this investigator concluded that the disappearance of corneal epithelium indicated that the aqueous humor was not a satisfactory nutrient medium and he pointed out that clinically blood vessels were always found in close approximation to epithelial ingrowths while epithelial cysts probably derive nutritional support from iris or other uveal tissue.

Recently Cogan, studying the reactions which occur when free pieces of conjunctiva are implanted in the anterior chamber of rabbit eyes, found that epithelium spread rapidly over the surface of the iris during the first few postoperative days but then ceased to grow.[25] This epithelium was multilayered, showed well-formed goblet cells, and sometimes extended into the iris crypts. In several instances epithelial cysts developed within the iris stroma, often associated with a spread of epithelium along the surface of the iris. On lens capsule the epithelial membrane was thin and attenuated, and it extended over the posterior surface of the cornea only in the presence of subadjacent conjunctival stroma. When an implant adhered to the cornea without any iris connection, the result was much as Gundersen described and the stroma was preserved but the epithelium disappeared. The lack of mitotic activity in epithelial cells within the anterior chamber led Cogan to believe that epithelial extension is not an active growth process but a spread by sliding and that a vascular substrate is needed if the epithelial cells are to remain viable.

*B. Inturned Flap of Conjunctiva or Cornea.*—In general, the epithelium of inturned

conjunctival flaps shows a great ability to proliferate in the anterior chamber. Suzuki reported the results of implanting an attached conjunctival flap into the anterior chamber of 66 rabbit eyes through limbal corneal incisions.[22] He found that the conjunctiva became adherent to the iris and for the first week or two after operation caused a mild reaction, with some new blood vessel formation and exudate within the flap. In time, however, the conjunctival flap shrank, but it never disappeared completely. "Epithelial production" was observed in 13 cases, and, although epithelium seen miscroscopically within the anterior chamber in 21 of 53 cases resembled that of human post-traumatic cysts, in only 5 was the cyst large enough to be observed clinically. Cysts could occur both in the iris parenchyma and between the iris and conjunctival flap. In Suzuki's illustrations the epithelium extending along the posterior cornea seemed to be separated from this surface by some kind of connective tissue.

In 1931 Corrado reported a somewhat different experience.[26] He found that a limbus-based conjunctival flap tended to be expelled from the anterior chamber and if retained was completely absorbed. Neither trauma nor prolonged hypotony was effective, and no epithelial proliferation was observed. Corrado then introduced corneal flaps into the anterior chamber of rabbit eyes and placed a celluloid strip between the edge of the wound and the flap for 15 days. Under these circumstances the corneal flap was preserved within the chamber and became adherent to the iris. Moreover, if it was placed against the anterior surface of the lens a spread of epithelium over the adjacent iris nearly always occurred. Corrado concluded that hypotony resulting from an open wound was necessary for the viability of the corneal flap and that epithelial proliferation occurred when epithelial cells were in contact with a smooth surface.

Perera in 1937 performed experiments upon the right eyes of eight rabbits.[10] He dissected a superficial corneal flap including epithelium and a thin layer of stroma and placed it in the anterior chamber through a keratome incision made beneath the flap. The eyes were removed at intervals from five days to four months. Perera found an immediate and rapid proliferation of corneal epithelium after the operation, but this epithelium gradually degenerated and disappeared. The corneal flap was absorbed within three weeks, and an anterior adhesion of the iris to cornea was formed.

*C. Ingrowth of Epithelium Along Gaping Wounds, Incarcerated Tissues, or Deep Sutures.*—In 1939, Terry, Chisholm, and Schonberg said that they had produced epithelization of the anterior chamber in 12 instances, using 30 laboratory animals.[15] No report of these experiments was given, but it was stated epithelium grew along the back of the cornea when endothelium was destroyed. These authors also said that they found that epithelium followed a suture track deep into the cornea but did not extend into the anterior chamber. These investigators believed that hypotony was not essential for the growth of epithelium and that carrying sufficient nutrition with the flap was not invariably necessary.

In 1951 Dunnington and Regan, in a study of the tissue reaction produced by sutures, reported the growth of epithelium into the anterior chamber along the track of a deeply placed nonabsorbable surgical (silk) suture.[27] This epithelium extended about a millimeter into the anterior chamber but produced neither the clinical nor the histologic appearance of true epithelial invasion.

Recently Binder and Binder, describing the effect of heparin and ethyl biscoumacetate (Tromexan ethyl acetate) on the healing of linear corneal incisions in rabbit eyes, agreed with Bick that anticoagulants inhibited the formation of the fibrinous coagulum formed by the secondary aqueous.[28,29] However, they also observed that in the presence of a serum prothrombin level less than 30% of normal early fibroblast formation was inhibited and epithelium was permitted to grow freely along the wound edges as far as the anterior chamber. In such eyes epithelium soon completely lined

both lips of a corneal incision, but in no instance did the epithelium invade the anterior chamber.

In summary, epithelial invasion of the anterior chamber has been produced experimentally by the implantation of an excised piece of conjunctiva and underlying stroma and by inturning a flap of conjunctiva. Such growth was seen when epithelium was in contact with iris, and frequently took the form called post-traumatic cyst of the iris. True epithelization of the anterior chamber has not been reported.

## Experiments

For these experiments the monkey was chosen because its eye closely resembles that of man.[30] The monkey sclera is thin, but the iris structure, the resiliency of the tissues, and the lack of a fibrinous secondary aqueous humor are desirable characteristics. In all instances the monkey was anesthetized with pentobarbital (Nembutal) intravenously and the operation was performed with use of a standard surgical procedure similar to that used by me for cataract surgery. After a 3 mm. limbus-based conjunctival flap was prepared, a limbal incision was made with keratome and scissors. A complete iridectomy was performed, because preliminary experiments had shown that in the monkey eye a peripheral iridectomy is not sufficient to prevent incarceration of iris tissue within the posterior lips of the incision. Two corneoscleral sutures, placed through the anterior half of the wound edges at 10 and 2 o'clock, were carried back through the conjunctival flap and were tied upon its surface. Except for specific purposes 000000 mildly chromicized absorbable surgical (gut) sutures were used. The eyes were removed at varying intervals after operation. They were fixed in celloidin, sectioned serially, and stained with hematoxylin and eosin. The following series of eyes were studied.

*I. Implantations of Conjunctiva and Cornea.*—For these experiments animals were divided into three groups. The variations in the standard operation were as follows:

Group A: In six eyes the epithelium on the lower surface of the cornea was gently removed with a curette or spatula, inserted into the anterior chamber through a small limbal incision, and laid upon the iris of the same eye. These eyes were removed 3 to 12 weeks after operation.

Group B: In six eyes conjunctival epithelium was freed as much as possible from the underlying stroma and was placed upon the iris of the same eye. The eyes were removed 4 to 12 weeks after operation.

Group C: In eight eyes a piece of conjunctiva, including stroma and epithelium and measuring approximately $3 \times 2$ mm., was inserted into the anterior chamber of the same eye and laid upon the iris. The conjunctiva was excised from the fornix-based edge of the prepared conjunctival flap. The eyes were removed and sectioned serially four to seven months after operation.

*II. Inturned Conjunctival Flap.*—In 22 eyes a limbus-based strip of conjunctiva approximately 3 mm. long and 1 mm. wide was separated from the conjunctival flap and inserted into the anterior chamber in the vicinity of an iris pillar. Because of the well-known tendency to evert, the conjunctiva was fixed with a superficially placed corneoscleral suture. The eyes were removed at intervals from 4 to 16 months after operation.

*III. Epithelial Growth Along Gaping Wound, Incarcerated Tissue, or Deep Suture.*—Group A: An attempt was made to produce a gaping wound by repeated wound rupture. The standard incision was modified by omitting the conjunctival flap and instead making a corneal incision at the limbus. This was done in order that the site of the incision could be seen more easily. In 12 eyes the incision was opened daily at the same site (e. g., adjacent to the temporal suture) with an iris spatula. Usually the wound could not be ruptured after 10 to 16 days. The animals were killed 8 to 10 weeks after operation.

Group B: Because of the associated trauma and inflammatory reactions, it was not possible to incarcerate lens capsule or vitreous within the wound. Instead, an iris pillar was prolapsed between the lips of the incision in eight eyes. The eyes were removed at intervals from 4 to 12 months after operation.

Group C: In these eyes the standard limbal incision was made but the corneoscleral sutures were placed through the entire depth of the corneal and scleral edge of the wound. The following variations were made: 1. In 12 eyes 000000 silk sutures were placed at the site of the complete iridectomy. 2. In eight eyes 000000 silk sutures were used and the corneal endothelium adjacent to the incision was scraped. 3. In 10 eyes 000000 mildly chromicized surgical gut sutures were used and the iris was caught on the suture between the corneal and the scleral bite. 4. In 12 eyes the iris was caught on a 000000 silk suture between the corneal and the scleral bite. These eyes were removed 1 to 12 months after operation.

## Results

*I. Free Implantations.*—Groups A and B: When corneal or conjunctival epithelium was placed on the surface of the iris, it quickly disappeared, causing no evidence of inflammation and no disturbance of the normal pattern of healing. No trace of epithelium could be found in histologic sections from eyes removed three weeks after operation.

Group C: When a free piece of conjunctiva was inserted into the anterior chamber, the results were very similar to those described by Cogan.[25] In one eye the implant formed a white ball which moved freely in the anterior chamber, while in most of the others a small white mass was seen attached to the anterior surface of the iris. In four cases one could see a fine membrane on the iris near the implant, and in one instance the membrane extended about 2 mm. onto the cornea. This membrane could be seen grossly four months after operation but showed very little growth during the following two months.

Histologic examination of three eyes showed that the conjunctival implant which lay on the iris had become an amorphous pink-staining mass surrounded by a thin attenuated layer of epithelial cells. There was moderate lymphocytic infiltration and a slight thickening of the iris stroma underlying the mass, but there were no other signs of inflammation. In four other eyes an extension of epithelium over the iris surface was present in varying degrees. Adjacent to the implant the epithelium covering the iris was several cells in thickness and contained a considerable amount of pigment. In two of these four eyes epithelium had extended across the anterior lens capsule in a thin layer. In these eyes the conjunctival stroma had largely disappeared and the residua was infiltrated with lymphocytes and other round cells. The extensions of epithelium along the iris frequently ended in a knob-like protuberance similar to that described by Cogan.[25]

Sometimes the epithelium extended around the angle of the anterior chamber onto the posterior surface of the cornea, and in one eye this epithelial layer spread onto the posterior cornea and ended in a knob-like formation (Fig. 1). Iris was present in the angle of the anterior chamber, and the epithelium had extended over it to reach the posterior cornea, but the epithelium had extended beyond iris tissue and in the vicinity of the cellular protuberance no iris tissue could be seen. In some sections the epithelium on the posterior cornea appeared to rest directly on Descemet's membrane, was composed of several layers and contained several mitotic figures. This is the eye which clinically showed a thin membrane on the posterior cornea.

*II. Inturned Conjunctival Flap.*—Epithelial growths were seen in 12 of 22 monkey eyes in which a strip of conjunctival flap attached at the limbus was turned into the anterior chamber. These growths always took a cystic form and appeared during the

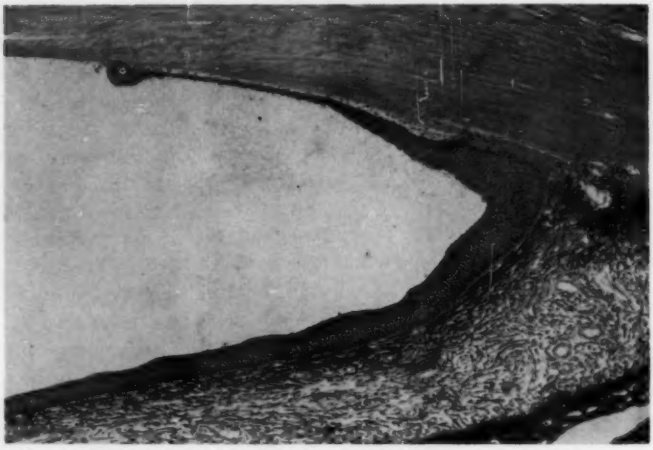

Fig. 1.—Monkey 14A, O. S. Epithelium within the anterior chamber seven months after implantation of free conjunctiva.

third or fourth month after operation as a fine membrane on the posterior cornea near an area of incarcerated iris tissue. Such lesions enlarged slowly, and at times growth seemed spontaneously arrested for the several months the animals were under observation. These cysts were well tolerated, and little evidence of inflammation was seen even when a cyst was very large. Both clinically and histologically these cysts resembled true post-traumatic cysts of the iris or anterior chamber. The incisions appeared firmly closed and ocular tension normal.

Microscopically the cysts were sometimes embedded in iris stroma but often filled the angle of the anterior chamber near the incision and frequently contained an acellular material which stained a faint pink color with hematoxylin and eosin and did not resemble the amorphous masses seen after a free conjunctival implant (Fig. 2). In eyes removed two to four months after operation the cysts were usually embedded in the iris stroma, and often a path of epithelium could be traced to them along the track of the wound (Fig. 3). After six months, when the cyst was usually larger and extended into the anterior chamber, the track of epithelium was seen less often but subconjunctival epithelial inclusion cysts were frequently present. The epithelium lining

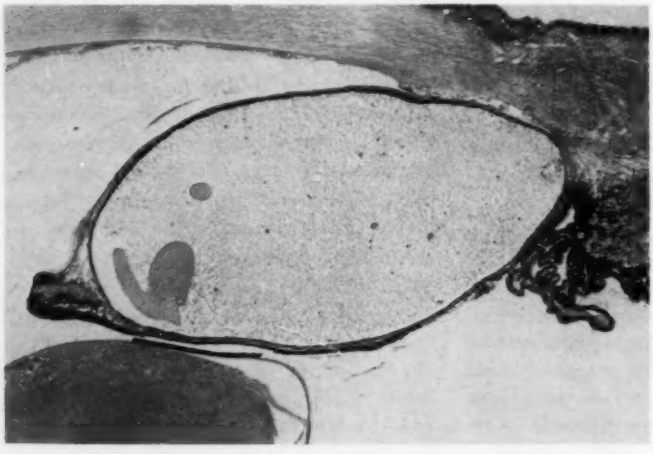

Fig. 2.—Monkey 54, O. D. Epithelial cyst of the iris 12 months after inturning of a flap of conjunctiva.

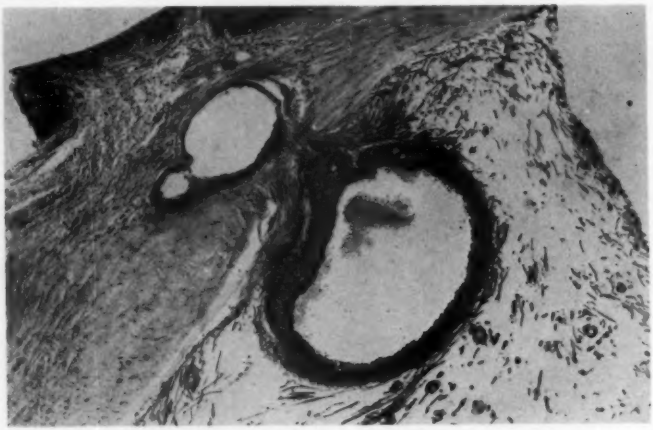

Fig. 3.—Monkey 5, O. D. Epithelium growing along incision four months after inturning of a conjunctival flap.

these cysts was usually cuboidal or columnar, but sometimes goblet cells were found. The viability of the epithelial cells was indicated by the presence of pigment and an occasional mitotic figure. When the cyst lay against the posterior cornea, there was often iris tissue between epithelium and Descemet's membrane. In general, the iris showed minimal round-cell infiltration with some thickening and pigment migration in the underlying stroma, but in one eye with a severe inflammatory reaction a multilobulated cyst involving both anterior chamber and iris grew rapidly and the eye became disorganized. Microscopically, extensive uveal inflammatory signs were found, the lens was cataractous, and epithelium filled most of the anterior chamber. In none of the eyes was conjunctival stroma seen extending into the anterior chamber.

When no cyst was formed, neither conjunctival epithelium nor stroma was seen in the anterior chamber but the anterior lips of the incision gaped widely and were filled with connective tissue and epithelial-lined cysts were sometimes present subconjunctivally or within the limbal incision.

*III. Ingrowth of Epithelium Along Gaping Wounds, Incarcerated Tissue, or Deep Suture.*—Group A: When a limbal incision without a conjunctival flap was ruptured, there resulted a marked irregularity of the wound characterized by an overgrowth of connective tissue similar to that described as stromal overgrowth by Levkoieva, Duke-Elder, and others.[31-34] Occasionally a few epithelial cells could be seen extending about half way through the incision, and only once was a small amount of epithelium found near the angle of the anterior chamber. These epithelial cells were completely blocked off from further extension by the exuberant growth of fibroblastic tissue from the corneal stroma and the sclera.

Group B: The trauma and inflammatory responses incited by incarceration of lens capsule or vitreous made this procedure unsatisfactory. Instead, iris tissue was left within the lips of the wound and the conjunctiva was closed over it in the usual manner. In only one instance was epithelial cyst found in the anterior chamber. A study of serial sections suggested that the conjunctival flap had turned into the anterior chamber along the edge of the prolapsed iris (Fig. 4).

Group C: When deeply placed mildly chromicized 000000 surgical gut sutures were used to close the incision, no epithelium grew along the suture track and there was no epithelial invasion of the anterior chamber. After six months only small clumps of mononuclear round cells were occasionally found at the suture sites. Epithelium grew rapidly along deeply placed 000000 silk sutures and often extended

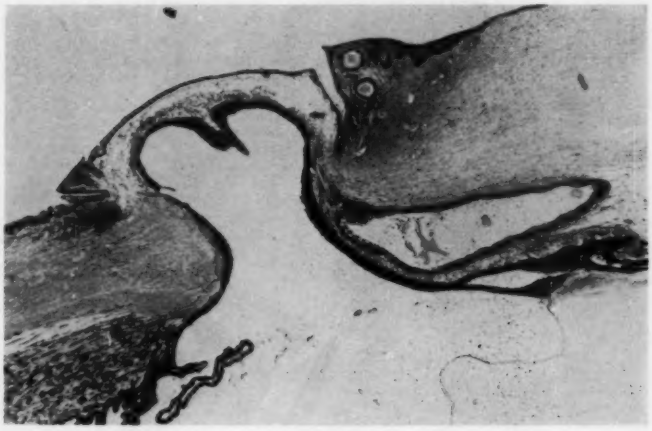

Fig. 4.—Monkey 10, O. D. Epithelium growing into the anterior chamber along prolapsed iris four months after operation.

throughout the depth of the wound. However, epithelium invaded the anterior chamber in only one instance. This was an eye in which vitreous had been lost at the time of operation and in which a lobulated cyst of the anterior chamber developed with surprising rapidity and was associated with a cloudy vascularized cornea and disorganization of the anterior half of the globe (Fig. 5). Another eye, removed 12 months after operation, showed no clinical evidence of epithelial invasion of the anterior chamber, but histologically epithelium extended along the suture track and reached the posterior surface of the wound in the area of the iridectomy (Fig. 6). In the 12 eyes in which the corneal endothelium was scraped and through-and-through 000000 silk sutures were used, no epithelial invasion occurred.

In contrast, when iris was caught on a perforating silk suture epithelium was present in 8 of 12 eyes. The clinical appearance was similar to that seen when a strip of conjunctiva is inserted into the anterior chamber. Histologically these epithelial growths resembled post-traumatic cysts of the iris or anterior chamber. In one eye which was removed 12 months after operation a cyst was observed over the nasal pillar of the iris at the end of 4 months. The cyst grew very little during the next few months, but a thin transparent membrane appeared on the back of the cornea adjacent to the cyst and near the incision and the

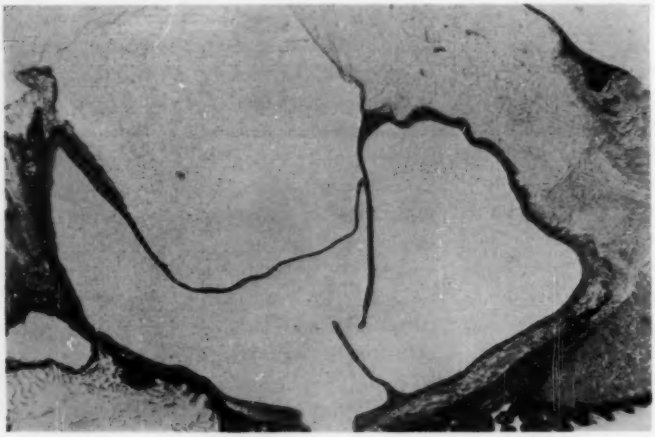

Fig. 5.—Monkey 52, O. S. Epithelial cyst of the anterior chamber eight months after operation. Deep silk sutures were used, and vitreous was lost at operation.

Fig. 6.—Monkey 12, O. D. Epithelium growing through the suture track two months after operation.

nasal pillar was caught up into the wound. Histologic examination showed iris incarcerated within the posterior lips of the wound. Epithelium extended over the iris to line the angle of the anterior chamber and spread onto the back of the cornea, ending in a knob-like protuberance (Fig. 7). The epithelium also extended over much of the iris and at times seemed to form lobulated cyst-like formations.

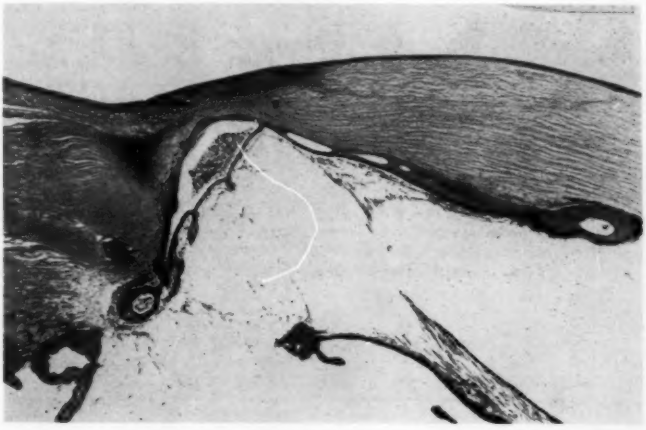

Fig. 7.—Monkey 50, O. D. Epithelium in the anterior chamber 11 months after operation. Iris was caught on deep silk suture at the time of operation.

| | Animal | Eye | Time After Operation | Epithelial Invasion | Remarks |
|---|---|---|---|---|---|
| I. Implantations | | | | | |
| A. Cornea: epithelium | 13 | O. D. | 3 wk. | No | Normal healing |
| | 13 | O. S. | 3 wk. | No | |
| | 14 | O. D. | 6 wk. | No | |
| | 14 | O. S. | 6 wk. | No | |
| | 15 | O. D. | 3 mo. | No | |
| | 15 | O. S. | 3 mo. | No | |
| B. Conjunctiva: epithelium | 46 | O. D. | 4 wk. | No | |
| | 46 | O. S. | 4 wk. | No | |
| | 47 | O. D. | 8 wk. | No | |
| | 47 | O. S. | 8 wk. | No | |
| | 48 | O. D. | 3 mo. | No | |
| | 48 | O. S. | 3 mo. | No | |
| C. Conjunctiva: epithelium & stroma | 11A | O. D. | 4 mo. | Yes | Epithelium covers amorphous stromal residua and adjacent iris and ends in a knob of cells; it extends over iris onto posterior cornea, ending as attenuated long thin cells; single layer of cells on cornea, multilayered on iris; cells contain pigment; some goblet cells |
| | 11A | O. S. | 4 mo. | No | Amorphous mass of stromal residua with few epithelial cells on surface |
| | 14A | O. D. | 7 mo. | No | Amorphous mass covered by single layer of epithelial cells |
| | 14A | O. S. | 7 mo. | Yes | Stromal residua infiltrated by mononuclear round cells; epithelium covers mass, extends onto lens surface & also over iris & onto posterior cornea, ending in knob-like protuberance; multilayered on iris, single layer on lens and cornea; on iris cells contain pigment; some goblet cells; moderate round-cell infiltration of iris |
| | 24A | O. D. | 7 mo. | No | Similar to 14A, O. D. |
| | 24A | O. S. | 7 mo. | Yes | Epithelium covers stromal remains and adjacent iris; cells contain pigment; no knob; increased pigment in underlying iris stroma |
| | 25A | O. D. | 5 mo. | Yes | Similar to 24A, O. S. |
| | 25A | O. S. | 5 mo. | No | Amorphous pink-staining mass; no epithelial cells |
| II. Inturned conjunctival flap | 3 | O. D. | 4 mo. | No | Epithelium extends to posterior surface of incision; separation of anterior third of wound filled with connective tissue; iris not involved |
| | 4 | O. D. | 12 mo. | Yes | 10 months after operation, fine membrane on posterior cornea; iris incarceration; lobulated epithelium-lined subconjunctival cyst at site of incarcerated iris; epithelial cyst in iris stroma; columnar epithelium fills angle of anterior chamber between incarcerated iris & posterior cornea; little uveal reaction |
| | 4 | O. S. | 12 mo. | No | |
| | 5 | O. D. | 4 mo. | Yes | Persistent injection of eye; hyphema 1 wk. after operation; anterior chamber became deep, pupil updrawn, tension low; large lobulated epithelium-lined cyst in iris containing some pink-staining substance; epithelial cells extend through incision and into stroma of iris adherent to incision; extensive mononuclear round-cell infiltration of uveal tissue; cataractous lens; cyclitic membrane; detached retina |
| | 5 | O. S. | 4 mo. | Yes | Iris prolapse, 1 wk. after operation; 2 small cysts in stroma of prolapsed iris; consist of 2 layers of epithelial cells containing a few pigment granules |
| | 10 | O. S. | 3 mo. | Yes | Iris adherent to posterior surface of incision; small cyst consisting of 2 or 3 layers of epithelial cells, in iris stroma |
| | 16 | O. S. | 1 mo. | No | Small epithelial cyst consisting of single attenuated layer of cells in iris stroma; no pigment in cells; iris adherent to incision |
| | 17 | O. D. | 2 mo. | No | |

*Summary of Findings*—Continued

| | Animal | Eye | Time After Operation | Epithelial Invasion | Remarks |
|---|---|---|---|---|---|
| | 17 | O.S. | 2 mo. | Yes | Irregular wound with iris incarceration; small cyst of single layer of epithelial cells between iris tissue and cornea; stromal overgrowth |
| | 22 | O. D. | 2½ mo. | Yes | Thin membrane on posterior surface of cornea 2 weeks after operation; did not change; very small epithelial cyst in iris stroma; iris adherent to line of incision |
| | 22 | O. S. | 2½ mo. | Yes | Cyst within iris stroma lined by several layers of epithelial cells; iris adherent to posterior surface of wound; few mononuclear cells in iris |
| | 23 | O. D. | 2 mo. | Yes | Epithelium-lined cyst in angle of anterior chamber near the incision; thin layer of iris between cyst and posterior surface of cornea |
| | 23 | O. S. | 2 mo. | No | Separation of anterior lips of the incision filled with loose connective tissue |
| | 25 | O. D. | 12 mo. | Yes | 3 mo. after operation: fine membrane on iris pillar; 6 mo.: iris cyst; no change, after this, in size; epithelium-lined cyst surrounded by iris stroma; several layers of epithelial cells containing pigment; small epithelial cysts along course of incision; thickening of iris stroma around cyst with little cellular reaction |
| | 25 | O. S. | 12 mo. | No | Iris adherent to posterior edge of incision |
| | 53 | O. D. | 5 mo. | No | 1 mo. after operation: pericorneal injection, cloudy cornea; 5 mo.: opaque cornea; shrunken globe; thickened cornea with loss of stromal structure; cataractous lens; cyclitic membrane; detached retina; stromal overgrowth |
| | 53 | O. S. | 5 mo. | Yes | 2 mo. after operation: small iris cyst; 3 mo.: cyst somewhat larger, fills about ⅓ of anterior chamber; 4 mo.: cyst growing; 5 mo.: cyst fills ½ of anterior chamber; large lobulated epithelium-lined cyst, sometimes surrounded by iris stroma; sometimes anterior surface rests on cornea; epithelial cells in 2 or 3 layers, contain pigment; goblet cells; iris stroma thickened at base of cyst; lens cataractous; retina detached; moderate uveal tissue reaction |
| | 54 | O. D. | 12 mo. | Yes | 2 mo. after operation: iris prolapse with fine membrane on back of cornea; 4 mo.: Cornea hazy with some vascularity in upper temporal quadrant; lens cataractous; 6 mo.: same; cyst lined by several layers of epithelial cells containing pigment fills ½ of iris; many goblet cells; much pink-staining matter in cyst; epithelium on iris surface & on posterior cornea near angle of anterior chamber; knob-like ending of epithelium; cornea: loss of stromal structure; lens: cataractous |
| | 14B | O. D. | 6 mo. | No | Similar to 23, O. S. |
| | 14B | O. S. | 6 mo. | No | |
| | 18 | O. D. | 16 mo. | No | Similar to 25, O. S. |
| | 18 | O. S. | 16 mo. | Yes | 4 mo. after operation: small cyst in anterior chamber; 6 mo.: cyst larger; 8 mo.: cyst fills ¼ of anterior chamber; 12 mo.: no change; epithelium-lined cyst fills ⅓ of anterior chamber; it rests on iris and extends to posterior surface of cornea; cells are several layers in thickness & contain pigment |
| III. | Epithelium ingrowth along | | | | |
| | A. Gaping wound (repeated wound rupture) | 1A | O. D. | 2 wk. | No | Epithelium extends deep into the wound but not into anterior chamber; extensive stromal overgrowth |
| | | 1A | O. S. | 2 wk. | No | Stromal overgrowth; iris prolapse |
| | | 2A | O. D. | 2 wk. | No | Similar |
| | | 2A | O. S. | 2 wk. | No | |
| | | 3A | O. D. | 9 wk. | No | |
| | | 3A | O. S. | 9 wk. | No | Stromal overgrowth; extensive detachment of Descemet's membrane |
| | | 4A | O. D. | 9 wk. | No | |
| | | 4A | O. S. | 9 wk. | No | |

*Summary of Findings*—Continued

| | Animal | Eye | Time After Operation | Epithelial Invasion | Remarks |
|---|---|---|---|---|---|
| | 5A | O. D. | 10 wk. | No | Similar to 1A, O. D. |
| | 5A | O. S. | 10 wk. | No | |
| | 6A | O. D. | 10 wk. | No | |
| | 6A | O. S. | 10 wk. | No | |
| B. Incarcerated iris tissue | 8G | O. S. | 8 mo. | No | Prolapsed iris covered by conjunctiva |
| | 9G | O. S. | 4 mo. | No | |
| | 10G | O. S. | 4 mo. | No | |
| | 11G | O. S. | 4 mo. | No | |
| | 7G | O. S. | 8 mo. | No | |
| | 4G | O. S. | 5 mo. | No | |
| | 12G | O. S. | 12 mo. | No | |
| | 10 | O. D. | 4 mo. | Yes | 2 mo. after operation: subconjunctival cyst; remained unchanged; iris prolapse partially covered by conjunctiva; epithelium extends between corneal side of incision & incarcerated iris into anterior chamber; goblet cells present |
| C. Deep suture | | | | | |
| (1) 000000 silk | 1 | O. D. | 1 mo. | No | Epithelial cells lining outer 2/3 of suture track |
| | 1 | O. S. | 1 mo. | No | Similar to 1, O. D. |
| | 11 | O. D. | 1½ mo. | No | Overlapping of wound edges |
| | 11 | O. S. | 1½ mo. | No | Epithelium extends deep into incision along suture track; much cellular reaction |
| | 12 | O. D. | 2 mo. | No | Irregular cord of epithelial cells extend through suture track to posterior surface; iris not involved |
| | 27 | O. D. | 12 mo. | No | Normal healing |
| | 27 | O. S. | 12 mo. | No | Lens cataractous; uveal inflammation; retina detached |
| | 50 | O. S. | 11 mo. | No | |
| | 51 | O. D. | 9 mo. | No | |
| | 51 | O. S. | 9 mo. | No | |
| | 52 | O. S. | 8 mo. | Yes | Vitreous loss at operation; 3 mo. after operation; small cyst in anterior chamber, iris prolapse; 5 mo.: cyst larger; cornea hazy; 8 mo.: cornea opaque; anterior half of globe disorganized; lobulated cyst lined with several layers of epithelium fills most of anterior chamber and extends behind iris; few goblet cells; lens cataractous; considerable cellular infiltration in iris |
| | 28A | O. S. | 1½ mo. | No | |
| (2) 000000 silk, endothelium scraped | 15B | O. D. | 4 mo. | No | Epithelium extends deep into incision along suture track; no other abnormalities in wound healing |
| | 15B | O. S. | 4 mo. | No | |
| | 9A | O. D. | 6 mo. | No | |
| | 9A | O. S. | 6 mo. | No | |
| | 12A | O. D. | 5 mo. | No | |
| | 12A | O. S. | 5 mo. | No | |
| | 22A | O. D. | 6 mo. | No | |
| | 22A | O. S. | 6 mo. | No | |
| (3) 000000 mildly chromicized surgical gut, iris caught on suture | 2B | O. D. | 1 mo. | No | Well-healed incisions; iris incarcerated in wound |
| | 2B | O. S. | 1 mo. | No | |
| | 9B | O. D. | 9 mo. | No | |
| | 9B | O. S. | 9 mo. | No | |
| | 11B | O. D. | 8 mo. | No | |
| | 11B | O. S. | 8 mo. | No | |
| | 25B | O. D. | 5 mo. | No | |
| | 25B | O. S. | 5 mo. | No | |
| | 19B | O. D. | 12 mo. | No | |
| | 19B | O. S. | 12 mo. | No | |

*Summary of Findings*—Continued

| | Animal | Eye | Time After Operation | Epithelial Invasion | Remarks |
|---|---|---|---|---|---|
| (4) 000000 silk sutures, iris caught on suture | 8 | O. D. | 4 mo. | No | Broad scar; overriding of wound edges; iris incarceration |
| | 8 | O. S. | 4 mo. | Yes | Cyst-like growth of cuboidal epithelial cells lines the angle between iris and cornea; epithelium extends over posterior cornea for short distance; knob-like ending of epithelial membrane on iris in some sections |
| | 12 | O. S. | 2 mo. | No | Iris prolapse |
| | 19 | O. D. | 1 mo. | Yes | Epithelium extending along suture track & onto iris for a very short distance |
| | 19 | O. S. | 1 mo. | Yes | Epithelial cells between cornea & iris in angle; epithelium along suture track |
| | 20 | O. D. | 2 mo. | Yes | Solid clump of epithelium in iris stroma |
| | 20 | O. S. | 2 mo. | No | |
| | 28 | O. D. | 3 mo. | Yes | Small cyst lined by 2 layers of epithelial cells embedded in iris stroma; minimal iris reaction |
| | 28 | O. S. | 3 mo. | Yes | Cyst in iris, lined by epithelium containing pigment granules |
| | 50 | O. D. | 11 mo. | Yes | 2 mo. after operation: small membrane over incarcerated iris pillar; 4 mo.: small iris cyst; 7 mo.: membrane extending from cyst over posterior cornea near incision; 11 mo.: membrane unchanged; epithelium in angle of anterior chamber extending from site of iris incarceration across posterior surface of incision; growth not globular, contains cystic portions, ends with knob-like protuberance; epithelium largely separated from posterior cornea by a few strands of iris stroma |
| | 52 | O. D. | 10 mo. | Yes | Epithelium-lined cyst embedded in iris stroma |
| | 54 | O. S. | 12 mo. | Yes | 5 mo. after operation: cyst in anterior chamber; 8 mo.: cyst larger; 12 mo.: cyst fills upper ⅓ of anterior chamber; large lobulated cyst in iris, lined by several layers of epithelial cells; mononuclear round cells in iris stroma; thickening of stroma near cyst |

## Comment

An analysis of epithelial invasion of the anterior chamber may be divided into three parts: (1) the means by which epithelium enters the anterior chamber, (2) the nutritive support for epithelium within the chamber, and (3) the production of epithelial growths.

An important influence upon these factors is the tendency for epithelial cells to spread widely or until they encounter other epithelial cells. In 1896 Ranvier, studying the healing of abrasions of rabbit corneas, described the mechanical slide of epithelial cells to cover a denuded area of cornea.[35] Since that time, the problem has been discussed by many investigators, including Matsumoto; Arey and Covode; Buschke, Friedenwald, and their associates, and Mann and her co-workers.[36-42] We know that corneal and conjunctival defects are readily closed by a sliding of epithelial cells across the denuded area. The process of epithelial spread begins within an hour after injury, progresses rapidly, and is eventually reinforced by active mitosis in the deepest layers of the epithelial cells. Since their spread is evident long before the establishment of fibroblastic proliferation, any separation of the wound edges is rapidly filled with epithelium. If the defect is large, the cells extending over the surface become flattened and attenuated, as if to cover as much space as possible. This condition may be seen both pathologically and experimentally when epithelial ingrowths extend across the lens capsule, the anterior hyaloid, or, less frequently, the posterior surface of the cornea.

In 1918 Matsumoto, studying epithelial movement in full-thickness corneal strips excised from frog eyes and suspended in a medium of plasma or serum, described two types of epithelial spread, both of which appeared between the 3d and 10th hours after excision and continued for the next 3 or 4 days.[36] The first only occurred when the corneal strip was suspended in plasma and consisted of an active ameboid-like spread of epithelial cells into the surrounding medium as a sheet or membrane whose extent and direction varied with the consistency of the plasma and the fibrin within it. In the second type of spread, which was more pronounced in serum, there was no ameboid motion or sheet-like extension into the medium but a marked tendency for the cells to cover the cut edges of the corneal strip and slide over the endothelial surface until the entire corneal fragment was covered by epithelium. Matsumoto also demonstrated that epithelium spread with equal if not greater rapidity over any smooth surface, including glass and fibers of spider webs and silk. In 1939 Thygeson reported the in vitro growth of human corneal and conjunctival epithelium.[43] He showed that cells from either site spread rapidly into the culture medium and by the end of 48 hours formed an extensive continuous sheet of epithelium. This type of epithelial spread is in many ways similar to that seen by Corrado,[26] Cogan,[25] and me.

Howes has emphasized the characteristic tendency of epithelium to extend across a denuded area until epithelial surfaces meet, at which time cellular spread ceases.[44] More recently, Gillman and Penn, studying the healing of skin wounds in rabbits and humans, have demonstrated that epithelial proliferation within the wound edges and along the suture track continues until the advancing epithelial edges meet.[45] This reaction occurs during the first eight days after operation and excites periepithelial round-cell and "fibrotic" reactions which in turn lead to the eventual disappearance of most of the subcutaneous epithelial clumps.

From such experimental studies we know that epithelium extends rapidly over a nonepithelized surface. This growth, which is largely by cell spread rather than by cell division, may be influenced by the consistency of the surrounding media, by the surface of the underlying tissue, and by obstacles in the pathway of the advancing epithelial border. Meller's famous pathologic report of epithelization of the anterior chamber four days after cataract extraction is an example of rapid epithelial growth, and numerous clinical and experimental investigators have indicated that smooth surfaces such as lens capsule, vitreous, and silk suture material provide an excellent means by which epithelium is able to gain access to the anterior chamber.[9,27,46]

Experimental and clinical studies show that corneal or conjunctival epithelium has access to the anterior chamber either by ingrowth along the wound edges or a suture track or by direct implantation. Although the latter method gives fairly consistent experimental results, it has less clinical importance. Implantations of conjunctival and corneal epithelium occur after trauma and in general produce cysts of the iris or anterior chamber. Theobald and Haas [16] suggested the folding of a conjunctival flap into the anterior chamber as an important method of producing epithelial invasion of the anterior chamber, and this has been confirmed experimentally by Suzuki [22] and by me. Both Suzuki and Corrado found that a conjunctival flap has a remarkable tendency to evert from the incision, and it was my experience that this tissue remained within the anterior chamber of the monkey eye only when sutured into the wound.[22,26] Clinically this is an unlikely happening, but a parallel situation might occur if a narrow conjunctival flap became incarcerated at the end of a limbal incision or when corneoscleral sutures are so placed that only the corneal arm is above the conjunctival flap. In this case, conjunctiva could be buckled into the wound, producing anterior gaping and a potential source of epithelial invasion of the anterior chamber.

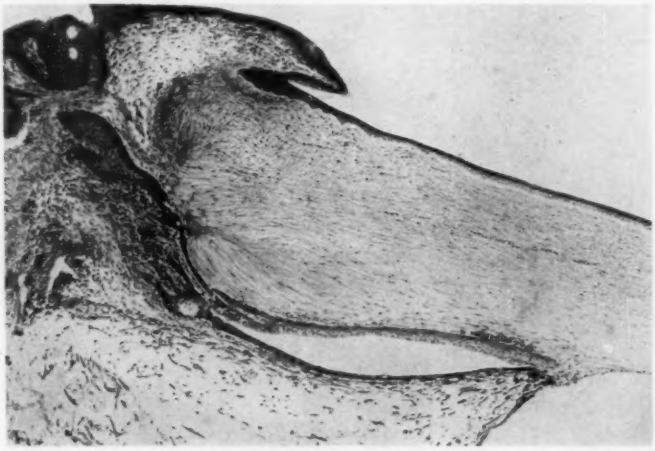

Fig. 8.—Monkey 8, O. S. Epithelium extending along the track of a suture four months after operation.

The rapidity with which epithelium spreads along a smooth surface is demonstrable by Figure 8, illustrating epithelial extension into the anterior chamber and iris along the track of a silk suture, while Figure 5 shows the extensive growth of epithelium within the anterior chamber after operation complicated by vitreous loss. The spread of epithelium along vitreous strands may explain the growth of cysts or epithelization in the anterior chamber after needling operations or perforating corneal injuries.

Once epithelium has reached the anterior chamber, there arises the problem of sufficient nutritive support for its maintenance. In my experience epithelial cysts or spread along iris or posterior cornea occurred only in those eyes in which epithelium was in direct contact with iris tissue. Figure 6 shows epithelium on the posterior surface of the incision one year after operation. There has been no multiplication or extension of the epithelial cells, in contrast to cyst formation and spread along the tissue surfaces when epithelium is in contact with iris (Fig. 9). This characteristic was mentioned by Maumenee and Shannon, who observed that epithelium usually spreads much more rapidly over the iris than on the posterior surface of the cornea.[13]

There is evidence that the aqueous humor per se is an unsatisfactory medium for tissue growth. Gundersen believed that this fluid did not supply sufficient nourishment for corneal epithelium and pointed out the frequency with which blood vessels are found in close approximation to areas of epithelization of the anterior chamber, while Cogan has said that to remain viable in the anterior chamber epithelium requires a "vascular substrate," to which it need form no tissue connection.[24,25] The need of a vascular substrate for continued tissue growth within the anterior chamber is also supported by studies of tumor tissue transplantation. Towbin has classified the reactions of tumor tissue in the anterior chamber in three stages: (1) the suspension stage, in which the transplant obtains its nourishment from the aqueous humor as it would in tissue culture; (2) the nidation stage, in which the tumor tissue receives nutritive support from the vascular system of the iris, and (3) the ensuing growth stage of the tumor tissue.[47] Albrink and Wallace, evaluating the aqueous humor of adult cats as a tissue-culture nutrient, found that pure aqueous humor supported survival but only limited growth of chick fibroblasts.[48] From their observations these investigators suggested that successful intraocular tissue transplantation depends on the ability of the aqueous humor to maintain cells for relatively long periods of time or until vascularization occurs and continued

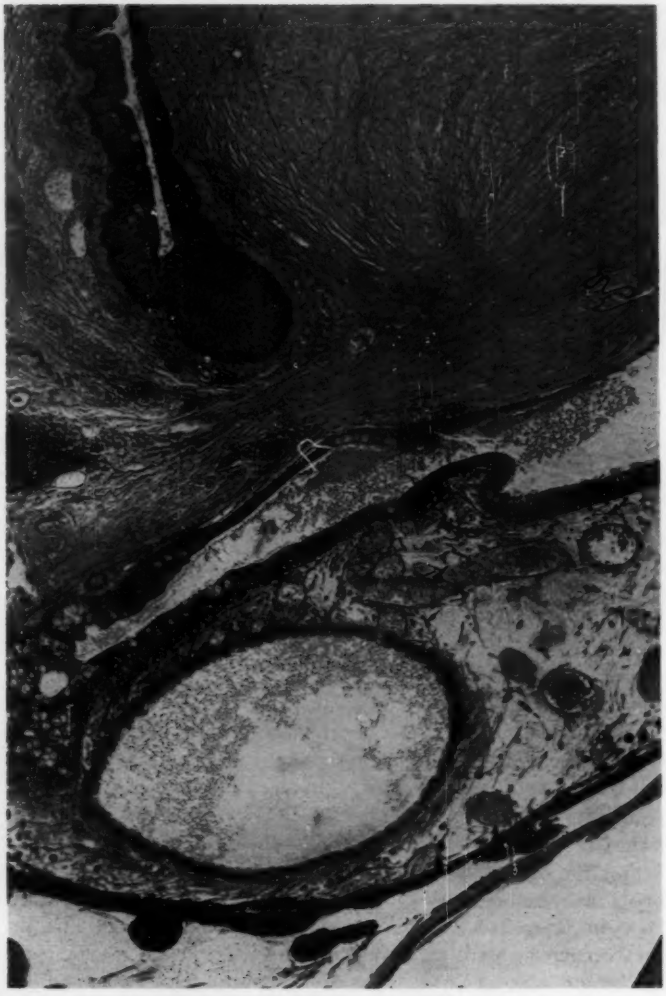

Fig. 9.—Monkey 25, O. D. Epithelium in the anterior chamber 12 months after operation. Conjunctival flap was inturned at time of operation.

growth ensues. Whether the plasmoid secondary aqueous humor that may occur with hypotony or iridocyclitis may provide a better nutritive medium for epithelial growth is not clear, but Matsumoto's experiments suggest that this may be the case.[36]

Epithelial invasion of the anterior chamber after keratoplasty operations is a rarity. Paton has said that he has never observed this complication, and no mention of it is made in Offret's discussion.[49,50] Furthermore, Hervouet demonstrated epithelial proliferation on the edges but not on the posterior surface of a corneal graft and Arkin, after inserting a corneal graft with its epithelial surface placed inward, could not demonstrate epithelium within the anterior chamber of a rabbit eye, despite the fact that the graft healed well.[51,52]

Only two of the monkey eyes with epithelium within the anterior chamber showed lesions suggestive of epithelization. In these eyes epithelium extended from the wound back over the iris and forward over the posterior cornea without intervening iris tissue and ended in a rounded protuberance

of epithelial cells (Fig. 1). However, there was little overlying change in the cornea and no evidence of glaucoma or uveal irritation. In contrast, epithelial cysts of the iris and anterior chamber can be produced with a good deal of regularity and may grow to involve most of the anterior chamber.

Maumenee and Shannon have said that there is a theory that epithelial cysts arise from a bud of epithelium pinched off in the anterior chamber and true epithelization arises from a migration of sheets of epithelium along poorly approximated wound edges.[13] There is no clear explanation for the appearance of a "post-traumatic" or epithelial cyst of the iris in one instance and epithelization of the anterior chamber in another, but one may theorize on the basis of experimental evidence. Matsumoto's investigations showed the facility with which epithelium extends over fibrin-like structures and the influence they have upon the direction taken by the advancing epithelial cells, and Howes has shown that the spread of epithelium ceases when two epithelial borders meet.[36,44] Moreover, Duke-Elder has suggested that epithelization differs from cyst formation because if tissue such as iris, stromal overgrowth, or lens matter is present it impedes epithelial proliferation and acts as a bed for cyst formation.[46] One may postulate that the presence of fibrin in aqueous humor may provide a better pathway for epithelial expansion and that epithelial cells advancing over the posterior cornea may grow across fibrin strands to the iris to meet the advancing border of the ingrowth, forming an anterior chamber cyst. As the fibrin strands contract the iris is drawn forward, producing a situation often seen in pathological eyes with epithelization after cataract extraction.

Experimentally the greater frequency of epithelial cysts of the iris may be caused by the deliberate attempt to insure the invading epithelium rapid and immediate access to iris tissue. One would then expect the epithelium to spread into the iris crypts, and cyst formations would result. The growth of these cysts in the monkey eye varied considerably, and some seemed to remain stationary for over a year while others were seen to enlarge steadily. Microscopically the epithelial cells lining the cysts usually contained pigment granules but mitotic figures were infrequent. The more rapidly growing cysts were multilobulated and usually associated with some microscopic evidence of iridocyclitis.

To compare the experimental invasion of epithelium with that occurring clinically a study was made of 77 eyes enucleated for various reasons related to epithelial growth within the anterior chamber. Epithelial invasion occurred after cataract extraction in 71 eyes, after perforating injury in 4, after iridectomy in 1, and after a perforating corneal ulcer in another. In this group of eyes the commonest clinical diagnoses were secondary glaucoma and iridocyclitis following catract extraction, but in 19 cases there was a definite history of hypotony. A positive fluorescein test was demonstrable in nine eyes, and in seven attempts had been made to close a fistulizing wound. A diagnosis of "post-traumatic" or epithelial cyst of the iris had been made before enucleation in 7 instances, and one of epithelization of the anterior chamber in 17 other eyes. One or more discissions had been performed on 11 eyes; an iris cyst had been removed from 4 eyes, and 9 had received radiation therapy. In two instances the cataract incision ruptured from a blow on the eye some months after operation and after enucleation epithelial invasion of the anterior chamber was found. Thirteen eyes had no symptoms of epithelial invasion for more than one year after operation or injury, and, of these, five showed clinical and pathological evidence of an epithelial cyst of the iris.

On histologic examination only nine eyes showed a well defined epithelium-lined cyst of the iris. In 18 eyes a knob-like protuberance marked the end of the epithelial membrane on the posterior corneal surface or on the iris, thus agreeing with descriptions of true epithelization of the anterior chamber.[13,25] The majority of the globes ex-

amined showed epithelium-lined cysts, often multilobulated, obstructing the angle of the anterior chamber, lying on the iris, and sometimes extending down into its stroma and attached to the posterior corneal surface with little or no intervening iris tissue. Anterior chamber cysts were occasionally diagnosed clinically as inclusion cysts of the iris but oftener were called epithelization of the anterior chamber. Many times an epithelial path could be traced through the incision to the anterior chamber cyst, and in one eye it was continuous with a subconjunctival epithelium-lined cyst.

Many of the epithelial growths in the anterior chamber resembled those produced experimentally in the monkey eye. The iris cysts were similar; small epithelium-lined iris cysts were associated with a spread of epithelium along the surface of the iris, and epithelium often lined the angle of the anterior chamber between cornea and iris when strands of the latter were adherent to the posterior edge of the incision. There was also much similarity between epithelial growths which involved iris stroma and extended into the anterior chamber as multilobulated cysts.

Both experimental and pathologic studies confirm Maumenee and Shannon's clinical observation that growth of epithelium on the iris is usually more extensive than that on the posterior cornea.[13] In all but one human eye iris tissue was involved in the epithelial invasion, and in this eye there was a small clump of epithelial cells resting on Descemet's membrane and more or less separated from the anterior chamber by an exuberant overgrowth of fibroblastic tissue from the lips of the incision. Although repeated paracentesis and wound rupture did not influence the experimental growth of epithelium in the anterior chamber, one cannot assume that these incisions closed promptly. Inturned conjunctival flaps, incarcerated iris, and perforating sutures tend to delay wound healing and prolong hypotony. The histories of the 78 human eyes studied and the clinical observations of many investigators also stress the role of improper and delayed wound healing in the production of epithelial invasion of the anterior chamber.

## Conclusions

Experimental and pathologic studies indicate that epithelium may invade the anterior chamber by implantation of free or attached epithelium or by spread along an irregular incision or smooth surface extending through the wound. Corneal epithelium could not be grown in the anterior chamber, but there is evidence to suggest that this can occur clinically. For epithelium to proliferate in the anterior chamber a more nutritious medium than the aqueous humor appears to be required, and this is obtained when epithelium comes in contact with iris tissue. Having established a supporting base on the iris, epithelium can spread by sliding over cornea, lens matter, and vitreous.

At this date, the best treatment of epithelial invasion of the anterior chamber is its prevention. The *sine qua non* for this is accurate approximation of the edges of any ocular wound. In cataract surgery other considerations are also present. The use of an oblique incision under a limbus-based conjunctival flap has been shown to prevent the ingrowth of epithelium along the wound edges and to promote good approximation and rapid closure by sealing of the wound by subconjunctival and episcleral tissue.[34] According to the present studies it would seem best to close the conjunctival incision separately to prevent incarceration of conjunctival tissue. The importance of freeing the lips of the wound from lens capsule, cortex, vitreous, or iris tissue has been stressed for years and needs no further discussion.

Dunnington has suggested that epithelial invasion of the anterior chamber has increased since the use of corneoscleral sutures, and Blodi has reported epithelial downgrowth as the cause of postoperative failure in 29% of 150 eyes enucleated after cataract extraction.[34,53] It has been advised that corneoscleral sutures be placed through

no more than the anterior half of the wound lips and that, to prevent infolding of the conjunctival flap, sutures should be buried or else both arms should be carried through the conjunctival flap before being tied. Moreover, epithelium is far less likely to grow along the track of mildly chromicized surgical gut than along that of silk sutures. Whether this is because of the smooth structure of the silk, as suggested by Matsumoto's work, or because of the difference in the cellular response to the two substances remains to be seen.[27,34,36,54]

## Summary

Experimental growth of epithelium was produced in eyes of Macaca mulatta (rhesus) monkeys. These growths resmbled cysts of the iris and the anterior chamber but in two instances showed some of the histologic but not the clinical characteristics of epithelization of the anterior chamber. To have epithelium grow within the anterior chamber the epithelial cells had to be in contact with iris stroma.

Seventy-seven enucleated eyes showing epithelial invasion of the anterior chamber were analyzed, and the importance of hypotony and improper wound healing in the production of this condition is discussed.

To prevent epithelial ingrowths after cataract extraction it is suggested that a limbus-based conjunctival flap be used and that its edges be closed separately by suturing. Corneoscleral sutures should not pass through more than half the depth of the incision and should be buried or else both arms should pass through the conjunctival flap before they are tied. Experimentally, epithelial ingrowth was produced when nonabsorbable (silk) but not when mildly chromicized absorbable (gut) surgical sutures were used.

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# Homonymous Macular Scotomata in Cases of Occipital Lobe Tumor

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Perimetric examinations of patients with cerebral lesions reveal many kinds of defects in the homonymous fields of vision.[1] Among the commoner ones are partial or complete anopias or ambylopias. Insular or discrete scotomata have been observed, but their incidence is low. An analysis of our cases has shown that in general the kind of defect one finds depends on the location and etiology of the lesion in the geniculocalcarine system.

In a previous communication it was stressed that patients with tumors of the temporal lobe showed a progressive change in vision from day to day when serial perimetric examinations were made. The earliest sign of impending hemianopia in temporal lobe tumors was either a loss of vision in the temporal crescent of one eye or impairment of perception of color in homonymous quadrant or half-fields of vision.[2] Later, these visual defects became more extensive and more definitive. After loss of color vision, brightness perception became diminished, and ultimately perception of motion was lost. In all of these cases the above changes in visual perception were first detectable in the periphery of the field and, as the neoplastic disease progressed, the disturbance spread toward the central isopters, until finally, the macula itself became involved.[3]

In our experience, cases of vascular lesions of the temporal lobe show the same type of visual field changes as those just described for cases of temporal lobe tumor. So far, we have not observed a single instance of discrete scotomata in vascular disease of the temporal lobe. In the cases of shrapnel or gunshot wounds of the temporal lobe which we have studied and which others have reported, there have been very few instances of homonymous scotomata. Since in most of these cases there have been no autopsy studies, one is not certain as to the exact site of the lesion, despite the fact that the direction of the penetrating missile and the x-rays localized the lesion to the temporal lobe. Holmes[4] has ". . . seen no case in which a paracentral scotoma, or an isolated affection of central or pericentral vision, could be attributed to a lesion of the radiation." In Spalding's series of 62 cases of battle injuries to the visual radiation there was only 1 patient with a lesion in the temporal lobe who showed macular scotomata. However, even in this case, the scotomata in the homonymous quadrants were surrounded by an area of amblyopia.[5,6] From the foregoing it is apparent that lesions of the temporal lobe, whether neoplastic, vascular, or traumatic, produce homonymous quadrant or hemianopic defects in the field of vision.

In studies of the occipital lobe one may find scotomata in the homonymous fields of vision. This is particularly true for cases of shrapnel or gunshot wounds of the occiput.[7] Other types of injuries, such as that produced by a ventricular puncture[8] and vascular lesions in the occipital lobes,[9] may also show scotomata. On the other hand, patients with tumor of the occipital lobe rarely manifest homonymous scotomata. The char-

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acteristic field defect in these cases is often a partial or complete anopia or amblyopia.[10] Until recently we did not find one case of occipital lobe tumor with scotomata in the homonymous half-fields. The purpose of the present paper is to present three patients with occipital lobe tumor, each of whom showed paramacular scotomata as a presenting symptom of visual defect.

CASE 1.—A 41-year-old executive complained that in October, 1954, his vision was not clear, in the sense that there was an intermittent haze between him and any target observed. Two weeks later he reported intermittent spots in front of his eyes and an inability to read. He had great difficulty in finding print, even words that he had written; in fact, even his own signature was not clear to him on occasion. Subsequently he could not see larger print, and these difficulties began to last for longer periods. At times he reported that figures and letters tended to merge on his right side. Neurologic examination on Dec. 31, 1954, was negative. On confrontation, the visual fields seemed normal, including perception of color, and tests with the American Optical Company isochromatic plates revealed no defects. That evening the patient had a severe left-sided headache. On Jan. 23, 1955, his vision, which until then had been fluctuating, became definitely worse. Print began to disappear, and at times vision was completely obliterated to the right. The neurologic examination on Feb. 2, 1955, was again negative, the visual fields appearing full on confrontation. Tests with the isochromatic plates, however, revealed a tendency to omit or erroneously report numbers in the right homonymous half-fields, the greatest difficulty being in the lower quadrants.

On Feb. 4, 1955, the plotted fields showed a distinct right inferior paramacular scotoma for the perception of a small, 1 degree, white target (Figs. 1*A* and 2*A*). Color and brightness perception in the remainder of the right half-fields was also impaired, but perception of motion and of large white objects was preserved. Vision continued to deteriorate, and three days later (Feb. 7, 1955) the scotoma showed a gradual enlargement, with only gross hand motion being perceptible in its vicinity (Fig. 1*B*). In addition, the patient began to complain

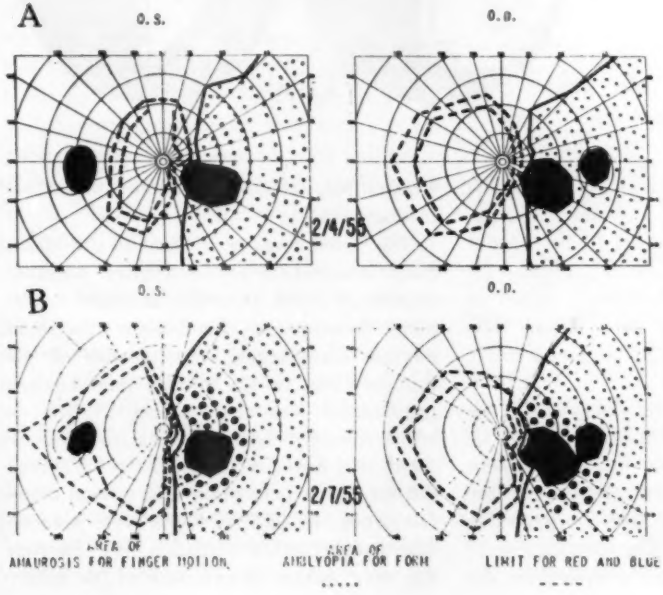


Fig. 1 (Case 1).—Recordings of tangent screen examinations. Note the enlargement of the paramacular scotoma three days after the first test. (The visual fields of Cases 1, 2, and 3 were charted on the dates recorded. Solid black indicates complete loss of all vision, including perception of motion. Stippled area is region in which there is perception of motion but not of form or color. Heavy stippling indicates an intenser defect. Lines of dashes represent boundaries of preservation of color vision.)

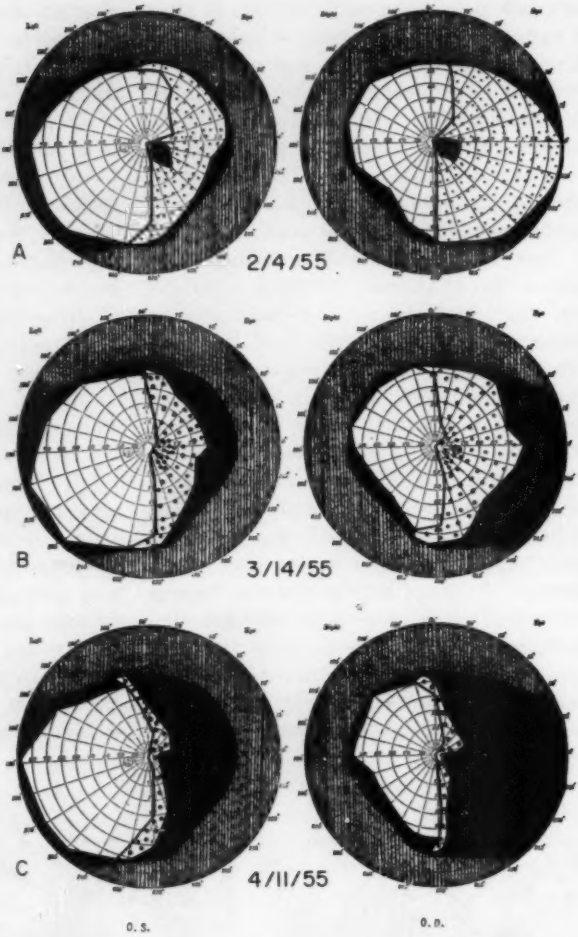


Fig. 2 (Case 1).—The recording of the perimetric examination disclosed the scotoma and the lack of perception of form and color in the rest of the field of vision, although motion was perceived to 90 degrees. Subsequent recordings of perimetric examinations showed increasing defects in the periphery of the field of vision (*B*). This defect progresses toward the center of the field. Also of interest is that the paramacular scotoma was well defined only in the early stages of the illness. On March 4, 1957, the scotoma was difficult to separate from the rest of the field. It seemed to merge with the surrounding perimacular area (*B*). Still later, the visual field showed a homonymous hemianopia with a scotoma in the macular region, yielding a sector-like defect (*C*).

of numbness, peculiarly enough, in the left hand. A brain tumor was suspected. The patient was therefore admitted to the Mount Sinai Hospital, where special studies, including a pneumoencephalogram, failed to reveal the presence of a mass lesion. The patient was discharged but remained under observation.

On March 14, 1955, the visual fields disclosed a right incomplete homonymous hemianopia, with only gross hand movement being seen in the paracentral isopters; the extreme periphery of the field was anopic to hand motion (Fig. 2*B*). The scotomata were no longer apparent at this time, because the paracentral defect had become dense and homogeneous.

The patient was readmitted to the Mount Sinai Hospital for further studies. Reexamination on April 11, 1955, disclosed a complete homonymous hemianopia for hand motion with sector involvement of the macula (Fig. 2*C*). At this time bilateral papilledema was also evident. When the entire macular regions, of the involved and intact half-fields, were tested for the threshold for flicker perception (the critical flicker frequency, or CFF), values were obtained which were within normal limits. Shortening the duration of exposure of the flicker-

ing light, however, produced a decrease in the macular CFF threshold which was greater than that seen in the normal subject. On tachistoscopic examination the patient consistently showed difficulties in identifying geometrical forms in his right half-field. In fact, his threshold, expressed as the minimal time necessary for correct form identification, was more than twice as long in the impaired half-field than in the "spared" half-field.

A left carotid arteriogram, performed on April 12, 1955, showed a "stain" deep in the left occipital lobe which was considered indicative of a mass lesion. Consequently, on April 15, 1955, a craniotomy was performed, and a glioblastoma multiforme subtotally removed from the left occipital lobe. This brought but temporary relief, for within four months the symptoms recurred, and in October, 1955, the patient died. An autopsy revealed recurrence of the tumor in the left occipital lobe and previous postoperative defect.

*Comment.*—This case illustrates that a patient with a tumor of the occipital lobe can have homonymous paramacular scotomata if he is examined early in the course of his illness. It is apparent, however, that these scotomata are not discrete and persist for only a relatively short period. Of theoretical significance is the finding that the area surrounding the scotomata was involved for the perception of form and color. Moreover, as the illness progressed, vision in the periphery of the field became more defective, leading to a concomitant disappearance of the scotomata. The March 14, 1955, examination, for example, shows clearly that when the hemianopic defect was conspicuous in the periphery of the field the scotomata were not readily demonstrable in the macular area. The last examination, of April 11, 1955, disclosed the conventional homonymous hemianopia, with sector defects in the right lower portion of the maculae where the scotomata had previously been plotted. An unusual symptom which should be noted in this case was the paresthesiae in the left hand, i. e., on the side ipsilateral to the gliomatous lesion.

CASE 2.—A 46-year-old accountant complained that during the last week of April, 1955, he had experienced periodic flashes of bright light in his right field of vision. On May 23, 1955, while he was in Florida attending a conference, there was a sudden onset of a series of flashing lights in the right visual field which persisted when he covered his right eye. This episode was followed by a period of approximately one hour during which time he was unable to recall what had happened. Persons present told him afterward that he seemed out of contact and was unable to recall the name of his wife or his address. He was hospitalized in Miami, Fla., where a neurologist stated that he had difficulty in naming objects. Within several hours he was fully oriented in all spheres. He no longer showed dysnomia and the attacks of flashing lights had stopped. For the first time, however, he noted a disturbance of vision which he described as a "hazy or cobwebby" appearance of objects to his right. Although this subjective visual complaint persisted, field examinations by an ophthalmologist on May 27, 1955, showed no abnormalities. No scotomata were found, and the acuity was reported as right eye 20/30, left eye 20/20.

Perimetric fields determined on June 2, 1955, disclosed a right homonymous defect for perception of a 1 degree white target, most marked in the superior quadrants (Fig. 3*A*). Perception of 1 degree color target was defective throughout most of the right half-fields, although some color perception remained in the lower quadrants. Tangent screen examinations of the same date revealed a small relatively delimited area of increased density for perception of white (3 mm. target at 330 mm.) in the right upper portion of the macula (Fig. 4*A*).

A neurologic examination on June 3, 1955, revealed occasional difficulty in naming parts of objects. However, he was able to carry out complicated commands involving body parts promptly and correctly, and

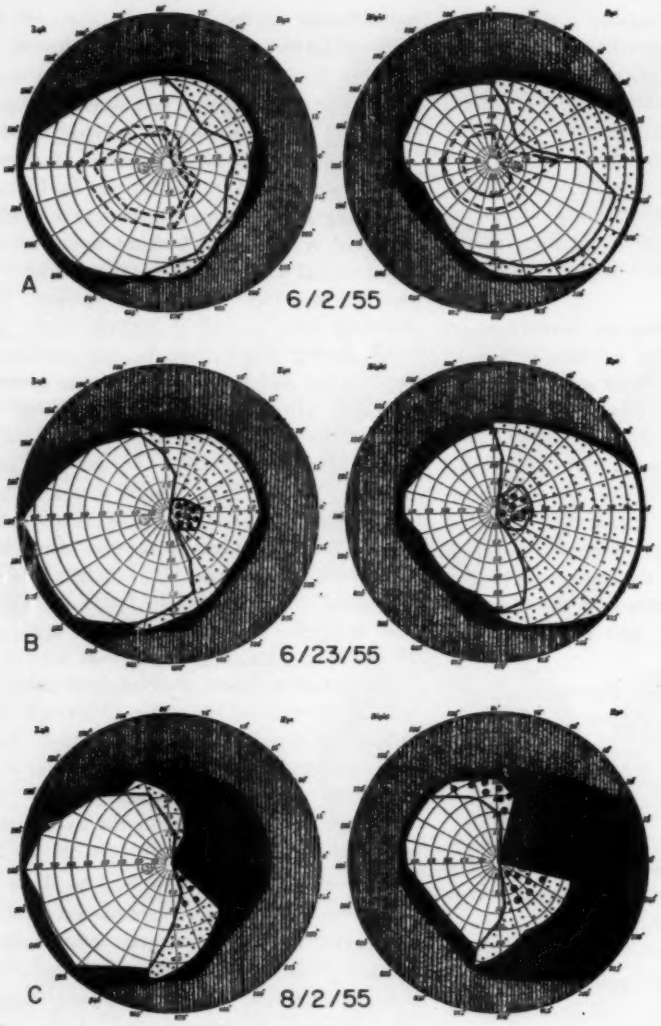


Fig. 3 (Case 2).—The charts illustrate the progressive nature of the two types of visual field defects. The perimetric examinations made over a period of two months demonstrate that the earliest defect occurred in the periphery of the field and progressed to implicate ultimately the central portions of the field of vision. However, an amblyopic defect appeared in the left homonymous portions of the macular and paramacular regions. Note the incongruity in the anopic portions of the field of vision.

he calculated well. A right homonymous field defect was present on confrontation. The rest of the neurologic examination was normal. An electroencephalogram revealed focal dysfunction over the left temporal-occipital area. Because of the progressive nature of his illness, he was admitted to the Mount Sinai Hospital, New York, on June 20, 1955, for special studies. The neurologic examination was negative except for defects in the homonymous fields of vision.

On June 23, 1955, the relative scotomata in the macular area were now more extensive and diffuse, while the remainder of the right half-fields of vision, particularly in the lower quadrants, showed defects (Figs. 3*B* and 4*B*). During this examination the patient suddenly reported the occurrence of "flashing lights" and localized them on the tangent screen as being in the right lower quadrant, extending from 5 to 15 degrees of parafoveal vision along the bisecting

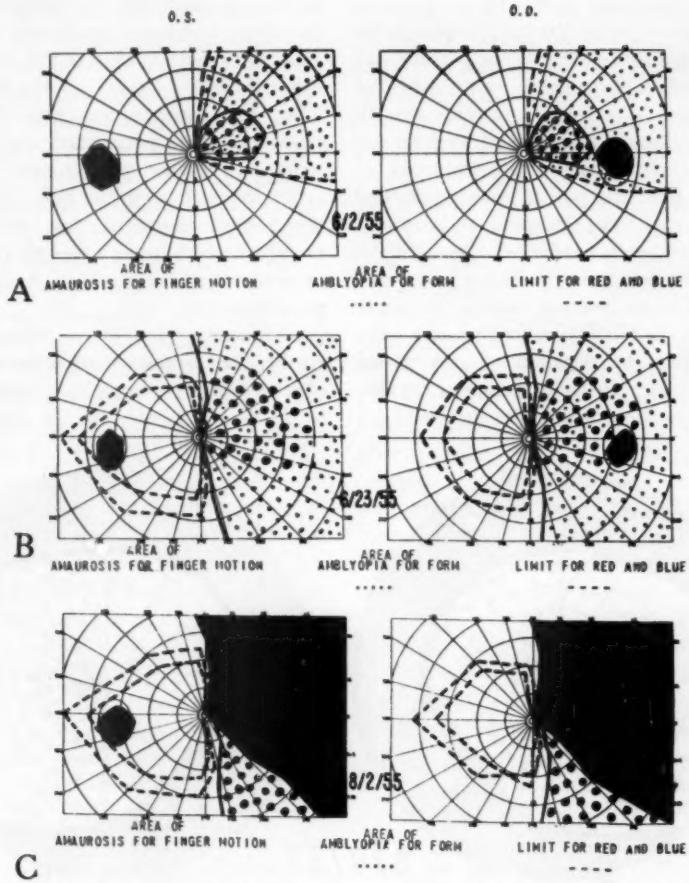


Fig. 4 (Case 2).—The tangent screen examinations of Case 2 reveal the nature of the spread of the macular scotomata. Note that on June 2, 1955, the scotoma in the macula was apparent on tangent screen (*A*) but could not be demonstrated on the perimetric portion of the field of vision (Fig. 3*A*).

meridian. A pneumoencephalogram, performed on June 28, 1955, failed to disclose a space-occupying lesion. He was therefore discharged from the hospital and kept under observation. The flashes of light persisted, but there were no new symptoms until the first week of August, 1955, when he became somewhat drowsy. He then complained of pain in the left temple, photophobia, and increased difficulty with vision. Visual field tests on Aug. 2, 1955, disclosed a right homonymous hemianopia, incomplete, with macular indentation in the superior quadrants (Figs. 3*C* and 4*C*). Note that the defects in the fields of vision are incongruent. At this time the scotomata could no longer be demonstrated. He complained of severe left-sided headache, and vision became worse. On Aug. 7, 1955, the patient complained of numbness in the first three fingers of the left hand. (It should be borne in mind that this complaint was similar to the one reported in Case 1.) The neurologic examination on Aug. 8 revealed blurring of the optic discs with a few small hemorrhages. There was now an almost complete right homonymous hemianopia upon confrontation. Somatosensory deficits were ob-

tained on the right side. There were no sensory deficits in the left hand, although the patient continued to complain of paresthesiae in this limb. There were some signs of aphasia, such as errors in naming objects, gross difficulties in reading and writing, and defects in performing simple calculations.

At this time the patient was readmitted to the Mount Sinai Hospital and detailed studies were again conducted. A slight decrease in the threshold for flicker perception was found in the macular region; this slight decrease in the CFF threshold became more marked when the duration of observation was shortened. On tachistoscopic examination a marked increase in the threshold for object identification was obtained in both the upper and lower quadrants on the right side. On Aug. 11, 1955, a left carotid angiogram showed a "stain" in the left occipital lobe. Consequently, on Aug. 16, 1955, a craniotomy was performed, and a glioblastoma multiforme was subtotally removed from the left occipital lobe. For a while the patient improved, but within a few months he became increasingly disabled and drowsy and ultimately died. An autopsy was not permitted.

*Comment.*—The above case illustrates further that homonymous scotomata may be observed in a patient with a tumor growing in the occipital pole. As the condition pro-

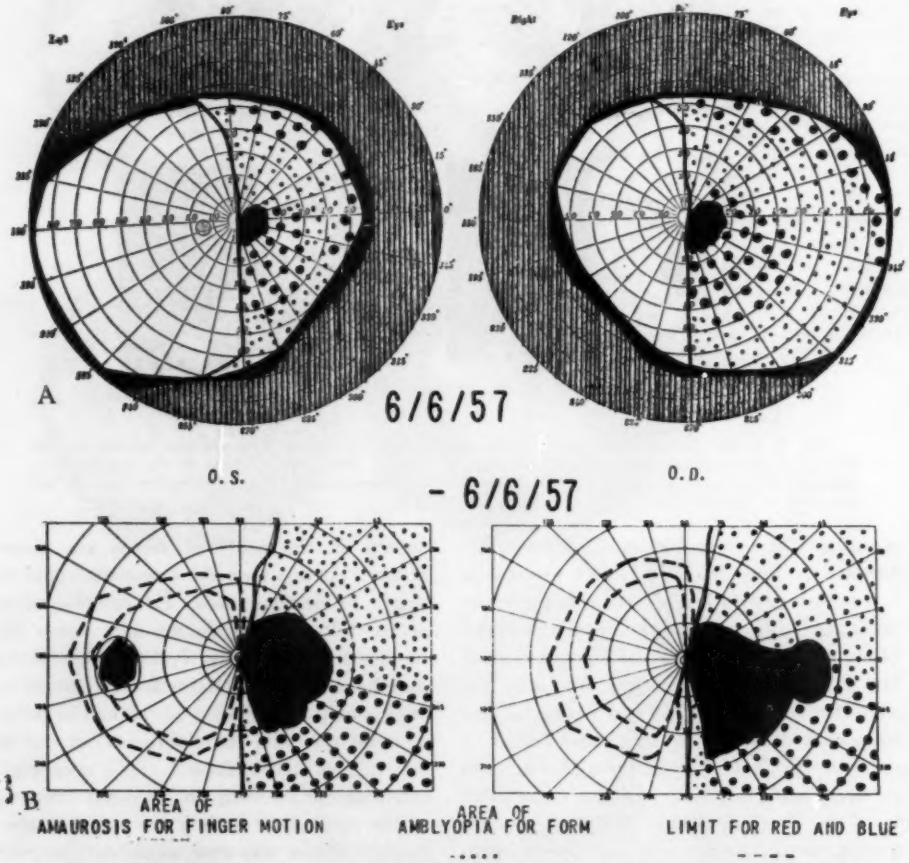


Fig. 5 (Case 3).—Repeated perimetric and tangent screen examinations disclosed scotomata in the homonymous left macular regions. The scotomata were surrounded by amblyopia in the left inferior quadrants.

gressed the peripheral deficits became more pronounced and the macular scotomata, less discrete. Ultimately, there developed a typical incomplete hemianopia with a macular sector in the superior quadrant, the same region where the scotoma had initially been plotted. It is noteworthy that this patient also complained of paresthesiae in the left hand, i. e., the side opposite to the hemianopia. The significance of this somatosensory phenomenon is not clear.

CASE 3.—A 47-year-old physician gave a vague history of visual disturbances. This information was obtained when by chance a perimetric examination disclosed an amblyopic defect in the right homonymous perimetric field of vision in April, 1957. After this, the patient was interrogated more closely, and the only data elicited were (*a*) that since 1953 he occasionally missed seeing an automobile passing on his right side while driving, (*b*) that he thought he might have had some trouble in reading for two years, and (*c*) that since 1952 he had had sporadic headaches occurring once in three months, the episodes lasting two to three hours.

The neurologic examination was entirely normal except for the defects in the field of vision. The fundi, pupillary reactions, and eye movements were normal. Repeated perimetric and tangent screen examinations over a four-week period failed to disclose any significant change in the size or nature of the defect (Fig. 5*A*). The scotomata and surrounding amblyopia were most pronounced in the inferior quadrants. He was able to see the color and form of large 1 in. targets, squares, or circles in the upper quadrants. One observer found an occasional error in naming of objects, but there were no significant signs of dyslexia, dysgraphia, or other manifestations of aphasia.

An x-ray of the skull showed a shift of a calcified pineal body from left to right. Repeated electroencephalographic tests disclosed a slight change in the left occipital lobe. Lumbar puncture showed clear cerebrospinal fluid under pressure of 160 mm. of water; it had a total protein content of 177 mg. %. Pneumoencephalogram revealed a mass situated in the left occipital-parietal region bulging into the posterior horn. The entire ventricular system was shifted from left to right. An arteriogram also disclosed a shift of the anterior cerebral artery from left to right. There were no abnormal vessels in the posterior circulation. At operation, on June 7, 1957, a meningioma 4.5 cm. in diameter was removed from the region of the torcular Herophili. The mass invaded the dorsal surface of the occipital lobe and the overlying dura, causing a defect 2.5 cm. in diameter. It pushed the occipital lobe downward and forward. Several hours after the operation, when the patient recovered from the anesthesia, there was a complete homonymous hemianopia upon confrontation.

On the first postoperative day gross visual testing showed some return of vision in the right upper quadrants, so that he perceived only motion in a small area; in the lower quadrants there was no perception of motion. On the second postoperative day he recognized outlines of large objects in the upper quadrants but still perceived no motion in the lower quadrants. On the third postoperative day he complained of seeing spots moving in the right upper quadrants from the left toward the midline. A few days later he noticed that these spots were in the lower temporal quadrant of the right eye and appeared as scintillating small lights. Subsequently he described these as "a row of arrows whose points were oriented in the vertical plane." There were three such vertical rows, all of which were constantly moving, in room light or in the dark, unless a bright light was projected into the right eye. With such a strong photic stimulus the scintillations were temporarily abolished and a large negative afterimage of the stimulating light appeared in the left half-field of vision of the right eye.

On June 19, 1957, the 12th postoperative day, perimetric examination showed a significant change. There was an increase in the size of the scotomata in the right ho-

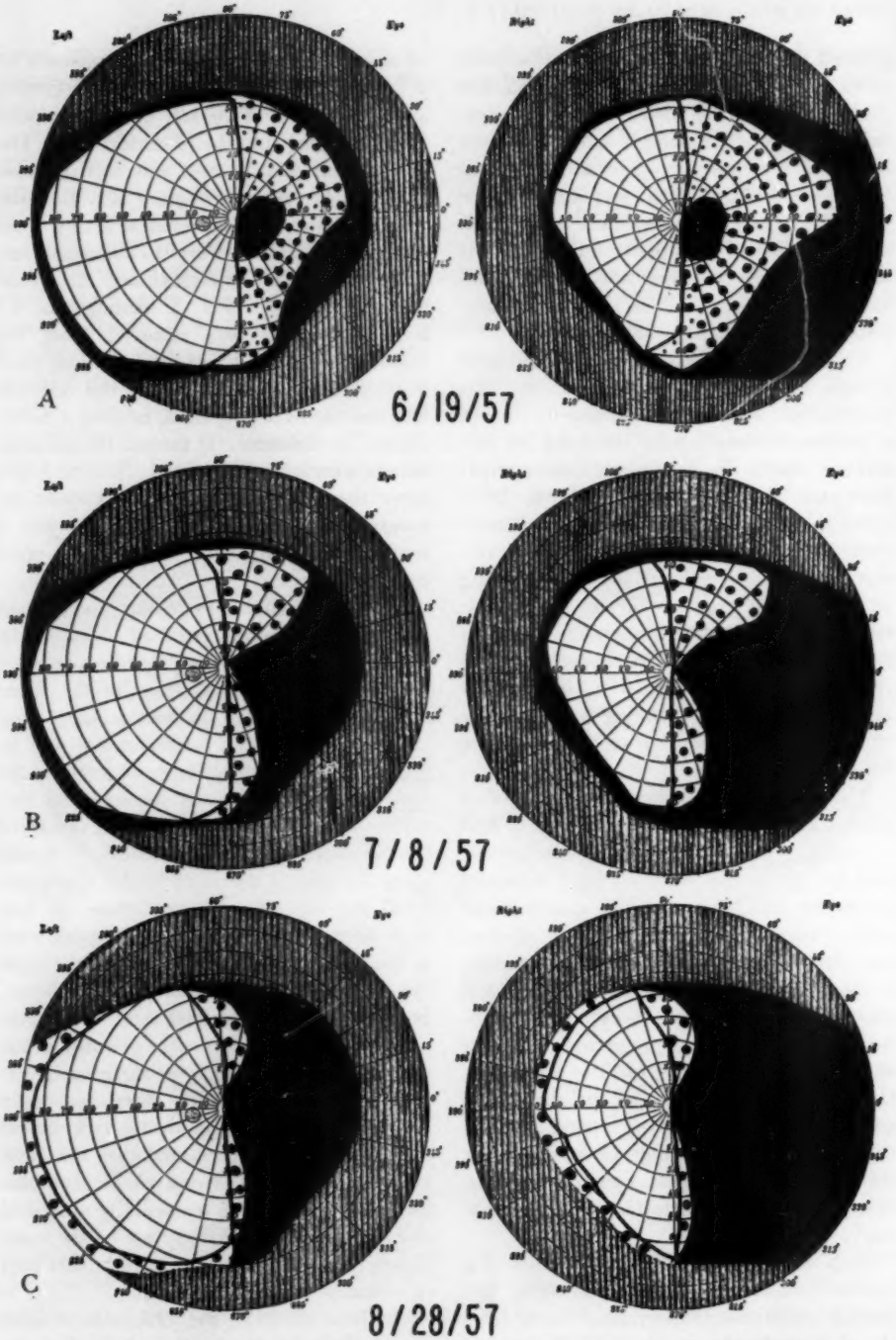


Fig. 6 (Case 3).—Postoperatively there was an almost complete homonymous hemianopia. As recovery continued, the defect receded from the center toward the periphery, but there remained a scotoma in the macular region of the right homonymous half-fields of vision, as indicated in *A*. Subsequently the defect became more extensive, so that the scotoma in the macular region merged with the advancing peripheral type of blindness, leading to a sector defect (*B* and *C*).

monymous macular areas as compared with preoperative fields. Correlated with the scotomata there was a visual defect in the peripheral part of the right half-fields, some motion being seen around the scotomata, none in the extreme periphery (Fig. 6*A*). Evidently the defect in the field of vision was getting worse instead of better.

On July 8, 1957, one month postoperatively, he complained of gross difficulty in reading because the "lines would get mixed up." Perimetric and tangent screen examinations on this date revealed an incomplete homonymous hemianopia with sector defects in the areas previously occupied by the scotomata. Some perception of motion remained in parts of the upper and lower quadrants on the right side (Fig. 6*B*). Reexamination on Aug. 28, 1957, revealed a further decrease in vision. The visual field tests now disclosed an almost typical homonymous hemianopia (Fig. 6*C*).

*Comment.*—This is the third instance of tumor of the occipital lobe with scotomatous defects in the homonymous paramacular zone of the field of vision. These scotomata were the first and only findings in this man's illness prior to surgery. Of interest is that immediately after operation the visual defect changed to the hemianopic variety. During the postoperative recovery period the defect lessened, so that the central scotomata and the peripheral hemianopic type of field defect were both apparent. Within a month, however, we were surprised that the patient became worse. The two different types of defects had merged, producing the classical picture of an incomplete homonymous hemianopia with a sector-like defect.

## Comment

In the present study we have shown that macular and paramacular scotomata can occur as a presenting or early symptom of occipital lobe tumor.* In all the three cases, however, these field defects were not isolated. The patients had homonymous areas of distinct amblyopia surrounding the localized scotomata. There was also gross impairment in color vision throughout the rest of the half-fields on the involved side. An exception was Case 3, where there was some residual color vision for large-sized targets prior to craniotomy. As the disease progressed in all cases, peripheral anopia became apparent with subsequent invasion of the already involved macular region, leading to an eventual homonymous hemianopia and apparent disappearance of the scotomata.

In each of the cases macular scotoma was replaced by a sector-like defect in the central portion of the hemianopia. These observations complement those of an earlier study on patients with relatively large temporal tumors and consequent involvement of the optic radiations.[3] In both the temporal and occipital cases the field defects progressed from the periphery to the macular area as the patient became worse. In short, regardless of locus of tumor, the pattern of visual loss over time was the same—from the periphery towards the macular area. Conversely, improvement in vision over time in temporal lobe cases was always first detectable in the center of the field and improvement progressed toward the periphery.[2] In the present study this occurred only in Case 3, during the first two weeks after operation. But here the initial scotomata could again be demonstrated in the macular areas. It should be noted that a similar type of recession was observed in patients with battle injuries or vascular lesions of the occipital lobe; improvement progressed from the center toward the periphery, but macular scotomata persisted.

Finally, in comparing the observations made in patients with neoplastic, vascular, or traumatic lesions of the geniculocalcarine pathway, one must conclude that (1) no distinction can be made between the gross quadrant or anopic field defects caused by lesions either of the temporal or of the occipital lobe, (2) the presence of scotomata

*Dr. Frank B. Walsh (Walsh, F. B.: Clinical Neuro.-Ophthalmology, Ed. 2, Baltimore, Williams & Wilkins, Company, 1957, p. 1048) mentions a case of homonymous scotoma in a patient who had a tumor of the occipital lobe.

in homonymous macular or paramacular zones is most characteristic of a lesion of the occipital lobe, and (3) sector-like defects in the central portion of a hemianopia may represent combinations of macular scotomata and peripheral type of field defects.

## Summary

Three cases of tumor of the occipital lobe with scotomata in the homonymous macular fields of vision are described.

The scotomata were surrounded by an extensive area of defective form and color vision.

As the tumor grew in all patients, defects in the periphery of the field of vision developed and progressed toward the center, so that in time the scotomata were not identifiable.

In one case the scotomata changed to a hemianopic type of field defect immediately after the operation. During recovery the hemianopia receded from the center toward the periphery, so that by the 12th postoperative day both the scotomatous and the peripheral or contracted type of visual defects were apparent. Later these defects combined to produce an incomplete hemianopia with a sector defect.

The significance of the type of defect in the visual field, namely, homonymous scotomata or hemiamblyopia, is discussed with reference to both locus and etiology of cerebral lesion.

The presence of scotomata in homonymous macular and paramacular zones is most diagnostic of an occipital lobe lesion.

Sector-like defects in the central portion of the defective field of vision are probably due to merging of the macular scotoma and the peripheral type of hemianopia.

Mount Sinai Hospital, 5th Ave. at 100th St. (29).

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## Case Reports

# Congenital Hereditary Horner's Syndrome

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The interest in this paper lies in the fact that the ophthalmologic literature reveals only vague and rare references to Horner's syndrome on a hereditary basis.

Duke-Elder,[1] mentions only that "rare hereditary and stationary form has been observed" and refers to von Michel,[2] 1903, and Oppenheim,[3] 1905. There are many references to congenital Horner's syndrome, but only Oppenheim [3] reports a case of a boy with typical Horner's syndrome whose mother showed the same findings. Calhoun [4] describes a family with typical Horner's syndrome in a description of heterochromia iridis.

My patient was a 2½-year-old child who was brought to the office for evaluation of a left ptosis. Examination revealed a ptosis of 3 mm. on the left, reduced size of the pupil, absence of sweating on the homolateral side, relative enophthalmos, and a blue iris on the left with a brown iris on the right. With use of cyclopentolate (Cyclogyl) the fundus was seen to be normal, with a minimal hyperopic correction.

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The parents of this child reported that the other members of the family showing a similar condition were the child's father, an aunt on the paternal side, an uncle on the paternal side, and one first cousin. Subsequent examination of these persons con-

Fig. 2.—Father, with slight ptosis on the left, although the iris colors are the same.

Fig. 1.—Present case, age 2½ years, with left narrowed palpebral fissure, left blue iris, and reduced left pupil.

Fig. 3.—Uncle, with left ptosis and difference in color of the iris.

firmed the diagnosis of Horner's syndrome, indicating the hereditary pattern. Complete examinations of these relatives were not carried out, but the Figures demonstrate the presence of the syndrome, although in varying degrees.

Professional Building, Augustine Cut-Off (3).

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# Fiberglas in the Eye

THOMAS R. GAINES, M.D., Anderson, S. C.

Fiberglas is the trade name of a product of Owens-Corning Fiberglas Corporation and is defined in their literature as follows:

"Basically, fiberglas is glass. Matter of fact, it is made in much the same manner as most glass. A number of finely pulverized ingredients, including sand, lime, and metallic oxides, are mixed in appropriate proportions and melted in a giant furnace. When the melting is completed, the mass is fused into a substance, glass, which is a complicated mixture of silicates, with no free silica present. The specific gravity is approximately 2.54. The molten glass is drawn out into slender, thread-like fibers. These flexible textile fibers look and feel like silk; the finest of them are almost invisible."

In a personal communication from the corporation's technical consultant it is stated: "The filaments are formed . . . for textile yarns by drawing slender filaments mechanically by means of rapidly revolving drums upon which they are collected. These fine filaments are flexible and practically continuous; however, some may break and some may purposely be made into short lengths by a hammermill process. The lengths of the shortest filaments may be upward from about two times the fiber diameter to whatever is desired for a finished lot of material for a particular use."

So far as I have been able to determine, there have been no reported cases in medical literature in which this material has penetrated the eye. Such a case is herewith detailed.

A white youth, aged 18, a "sliver" (glass filament) handler, got something in the left eye on Jan. 10, 1952, while handling "sliver" in a Fiberglas-manufacturing plant. He was seen shortly thereafter by the plant physician, who thought that he might have removed a small foreign body. The patient was seen the following day, and boric acid ointment was applied in the conjunctival sac. On the second day after the accident, Jan. 12, he was referred to me, and my associate saw him, making the note "large staining area left cornea," the vision being O. D. 20/20, O. S. 20/40. Atropine, 1% solution, was instilled, and 0.5% cortisone solution was prescribed to be instilled every hour. On Jan. 17, seven days after the accident, I saw the patient, at which time there was deep injection of the left globe, most marked around the limbus; there was a linear opacity of the cornea, about 2 mm. long, near the limbus at 11 o'clock, which appeared to extend obliquely into the stroma and possibly through Descement's membrane; there was a dot-like opacity of the lens just beneath the corneal opacity, which would fit in with a tiny foreign body having entered the anterior chamber, traversing the cornea and coming in contact with or entering the anterior lens capsule. However, a thorough search failed to reveal a foreign body. The remaining media were clear, and the fundus, normal. No cells were seen in the aqueous. Additional history at this time reveaied that a Fiberglas filament or fiber might have been thrown off of a "spiral" with much force and have struck him in the eye. Atropine solution was continued three times a day together with 0.5% cortisone instilled every two hours. He was seen at three- to five-day intervals, the eye continuing to have moderate ciliary injection, photophobia, and moderate discomfort.

On Feb. 2 slight corneal edema with swelling of the corneal nerves was noted and the vision had fallen to 20/100 in the affected eye. On Feb. 22 the vision was

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noted to be "O. D. 20/20, O. S. 20/100. No change in appearance of eye." Atropine was being continued twice a day, and cortisone, every three hours. On March 20 there was "still mild ciliary injection; vision 20/20 in each eye; media clear." On April 7, "the eye is now white, media clear, vision each eye 20/20," and it was thought he had entirely recovered, being allowed to return to work as of that date. On May 10 he returned, stating that he had noted discomfort and photophobia in the eye for three days. There was slight ciliary injection, with clouding in a circular area in the lower central portion of the cornea. The vision was O. D. 20/20, O. S. 20/60. Work was stopped, and treatment with atropine and cortisone as instillations was begun. On May 31 the corneal edema was increasing, the vision had deteriorated to 20/100, and it was thought best to hospitalize the patient for systemic cortisone therapy, in addition to local treatment of atropine, hot compresses, and cortisone. On the first day he was given intramuscularly 400 mg. of cortisone; on second day, 300 mg.; on the third day, 200 mg., and after this, 100 mg. daily for 12 days, during which time the redness and injection cleared remarkably and the eye became white and quiescent, the vision having returned to 20/20. On June 9, while a patient in the hospital, he was brought to the office and with the slit lamp a small filament of fiberglas was seen momentarily lying vertically in the anterior chamber, its lower pole being in the angle at 6 o'clock, its upper pole lying forward against the cornea (Fig. 1). While it was being watched, the upper end rolled over and the particle disappeared from sight in the lower angle. For the first time it was realized that a foreign body was present, more than five months having elapsed since it entered the eye, one month of which time the eye had enjoyed a period of symptom-free quiescence, allowing the patient to carry on his occupation in comfort. Since the eye was now quiet, with vision of 20/20, and the patient was comfortable, it was decided to allow him to return to work, which was

Fig. 1.—Schematic drawing illustrating position of the glass filament as seen lying loosely in the anterior chamber.

done on July 7, when all medication was discontinued. On Sept. 2 the vision was 20/30; the notes stated that the eye "remained a little irritated most of the time and is a little sensitive to light. Then he 'doubles up' on his cortisone and it gets better." There was a slight ciliary blush and faint corneal clouding. The particle of glass was again seen momentarily as before described. This eye continued to have periods of irritation, and the foreign body had been glimpsed on one or two other occasions with the slit lamp, always loose in the anterior chamber. Attempts had been repeatedly made to see it with the Goldmann gonioscopic prism, but these were not successful. On Oct. 6, 1952, the filament of Fiberglas was seen with the slit lamp in the same position as previously described. Physostigmine (eserine) was instilled in an effort to trap it in the anterior chamber, and the patient

was kept in an upright position until he was carried to the operating room. With use of local anesthesia, a fornix-based conjunctival flap was dissected up from 4 to 8 o'clock; a corresponding limbal trench incision was made, and McLean-type 000000 black nonabsorbable surgical (silk) sutures were carried through both lips of the wound and looped out of the way; a keratome was then carried through the trench wound into the anterior chamber at 6 o'clock, and the incision was completed with scissors. Attempts were made to see the foreign particle with the loupe, but it could not be visualized, nor could it be grasped blindly with the capsule forceps. A broad iridectomy was done from 5 to 7 o'clock, in hope that the filament might be found in the removed iris meshwork. As it was still not found, the anterior chamber was flushed with warm half-strength isotonic saline, which was likewise of no avail. The wound was closed, and a binocular bandage was applied for 48 hours. Recovery was uneventful, and on Nov. 11 the vision was 20/20 O. U., the eye being quiet. On Nov. 17, with the slit lamp, the foreign body was again seen in the same position, one end lying forward against the cornea and the other, in the lower angle at 6 o'clock. There was a ciliary blush and some corneal edema. Treatment was continued with scopolamine and cortisone instillations. The eye gradually became quiescent, and the patient was allowed to resume work on Jan. 14. On March 2, 1953, the filament of Fiberglas was easily seen lying against the ciliary processes in the iris coloboma from 6:30 to 7 o'clock with one end apparently fixed to the temporal pillar (Fig. 2).

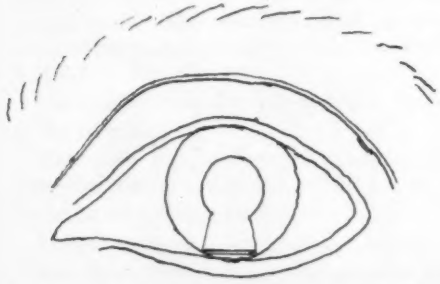

Fig. 2.—Schematic drawing illustrating Fiberglas filament attached to the temporal pillar of the iris coloboma. The foreign body was deeper in the recess of the angle than could be shown in the drawing.

The eye was clear and white, with normal vision, and the patient was working regularly. For a period of more than two years he was not seen, and it was concluded the eye had established a tolerance to the foreign material. However, on July 13, 1955, he came in, stating that the eye had again become uncomfortable; the vision was reduced to 20/100, there was slight ciliary injection, and the cornea was infiltrated in its lower central one-third. The reaction increased despite the usual treatment with corticosteroids and mydriatics, and on Aug. 17, 1955, the patient was hospitalized for a course of intravenous typhoid therapy. After 10 or 12 doses had been given, each of which produced a good reaction, the eye again became quiet, with vision of 20/20, and the patient returned to work on Sept. 9, 1955. On Nov. 11 he returned, stating that the eye had been reddened recurrently since the last visit. There was moderate ciliary activity and slight corneal edema, and the vision was O. D. 20/20, O. S. 20/60 slowly. The foreign body was again seen with the slit lamp lying horizontally in the lower angle from 5:30 to 6 o'clock. Activity continued despite treatment with corticosteroids and mydriatics. With the history of so many recurrences over so long a period of time and with the thought of a possible sympathetic ophthalmia in mind, it was decided that another attempt at removal should be made. On Nov. 18, 1955, with use of the usual local anesthetic agents together with Van Lint akinesia, lid sutures, and inferior and superior rectus sutures, a procedure similar to the one performed three years previously was carried out, except for the iridectomy. An Arruga capsule forceps was carried into the angle, cautiously following the temporal pillar of the coloboma, and was closed just where the foreign body had been visualized with the slit lamp. Fortunately, the filament was in the grasp and

was removed on the first attempt. It measured 4.5 mm. in length and was comparable to 000000 gut suture in diameter. The wound was closed, and the eye was bandaged. Recovery was uneventful. On Dec. 24, 1955, the globe was white, the media were clear, and the vision was 20/20.

## Summary

A case of intraocular foreign body consisting of a filament of glass (Fiberglas) is reported, the foreign material having remained within the eye for a period of 3 years 10 months.

Without explanation, there were periods of quiescence alternated with periods of activity, one period of quiescence having lasted more than two years without symptoms, during which time the patient worked uninterruptedly.

During the final four months previous to the removal of the foreign body, activity in the eye was such that it was believed that the point of tolerance had been reached and that there was danger of loss of the affected eye, with possible involvement of its fellow.

After removal of the foreign material the eye quickly became quiescent, with return of visual acuity to 20/20.

Professional Building.

# Intravitreal Parasite

SHREEMOHAN MISHRA, Balbhadrapur, India

The literature shows few authentic reports of intraocular parasites and still fewer reports of intravitreal parasites. In his textbook Duke-Elder [1] reviews as cases of intraocular parasites the reports of Wright, Fernando, Tawara, and Wilson. As cases of intravitreal parasites he gives the reports of Spanner, Nayar and Pillai, and Barrada. In 1945 Sen and Ghose [2] reported a case of ocular gnathostomiasis.

In this report the parasite has been provisionally labeled as an adult filaria (Wuchereria bancrofti). This has been done in view of the widespread infection of W. bancrofti locally and the morphological similarity of the reported parasite with the W. bancrofti. The only positive clinical finding, however, is a recurrent scrotal inflammation.

## Report of Case

The patient, a 21-year-old Hindu man, stated that on the morning of April 3, 1957, he noticed what seemed to be a small rod protruding before his right eye. He took a nap in the sun and upon awakening he noticed that the rod had become something like a serpent and that it was moving continuously before his right eye. He was aware of this even when he closed his eye. He presented himself for treatment on April 9, 1957.

On examination the left eye was found to be normal.

Externally the right eye was normal. Its corrected visual acuity was 6/12. J 1 type could be read with difficulty.

Ophthalmoscopic examination showed a filariform intravitreal parasite opposite the macular area and close to the retina. The worm, about 15 mm. in length, moved about in a brisk circular fashion. Its body, which reflected light brilliantly, was turned in two coils. One end of the worm seemed to be attached to the retina near the macula. The other end of the worm darted to and fro as its body coiled and uncoiled itself. This end of the worm was seen to be probing the subjacent vitreous and the area of the retina between the papilla and the macula. At times a dimple would appear in the retina at the point of the worm's probing. The worm's brisk movements caused the vitreous to appear rather hazy and at the same time to be filled with confusing light reflexes.

In spite of the difficulties created by the worm's movements, a central scotoma could be discerned. The retina in the macular and surrounding area was seen to be hyperpigmented and to have lost its normal red reflex. The choroidal vascular pattern was exposed in areas where the pigment epithelium had thinned.

The patient gave a history of recurrent attacks of redness, mild pain, and swelling of the left side of the scrotum dating from 1950.

Investigations for parasites, particularly microfilaria, produced negative results. Smear examinations of sputum, urine, stool, and skin were also negative.

On April 10, 1957, blood examination showed a total WBC count of 7900 per cubic millimeter; differential WBC count, 58% polymorphonuclear cells, 29% lymphocytes, 1% large mononuclear cells, 12% eosinophils, and no basophils. A repeat blood examination on May 3, 1957, showed the total WBC count to be 8600 per cubic millimeter, with a differential count of 48% polymorphonuclear cells, 39% lymphocytes, 1% large mononuclear cells, 12% eosinophils, and no basophils.

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Till April 16, 1957, the position of the worm remained more or less unchanged. On April 19, 1957, the movements ceased entirely, only to return again on April 24, when the worm moved to various other parts of the field of vision. According to the patient it would appear, disappear, and then reappear. An ophthalmoscopic examination done on May 1, 1957, showed the parasite swimming freely and briskly in the vitreous. For six months, until Nov. 30, 1957, the patient felt the movement of the worm for intermittent periods.

The patient was treated with (1) a penicillin and streptomycin preparation (Dicrysticin), 0.5 gm. i. m. daily for two weeks; (2) thiamine hydrochloride (Berin), 100 mg. i. m. daily for three weeks, and (3) chlorcyclizine (Histantine) hydrochloride, 1 tablet twice daily for two weeks. No vigorous antihelminth line of treatment was adopted for fear of stagnation of the worm in the macular area, with consequent devastating result on the visual acuity. The subsequent escape of the worm into the vitreous justified this line of therapy.

The case is still under observation.

Darbhanga Medical College, P. O. Laheria Sarai.

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Clinical Notes, New Instruments and Techniques

# Use of the Schepens Binocular Indirect Ophthalmoscope in Operations

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The remarkable advantages of the binocular indirect ophthalmoscope [1] * are becoming increasingly evident [2] as the instrument comes into wider and more proficient use.

In the treatment of retinal detachment the necessity for the recognition and precise localization of the tear, or tears, is axiomatic. This is true not only for the examining room but for the operating room as well.

One of the main uses of the ophthalmoscope is examination of the fundus during retinal detachment surgery, where the resultant findings guide the step-by-step progress of the operative procedure.

The procedure to be described deals with a method whereby the instrument may be detached from its headband and held in the hand as needed, thereby eliminating the necessity for wearing it continuously through-

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* Manufactured by the American Optical Company.

Fig. 1.—The binocular indirect ophthalmoscope, detached from its headband, draped for use during operation. In this photograph the towel draped about the handle has been pulled somewhat lower than usual, for demonstration purposes.

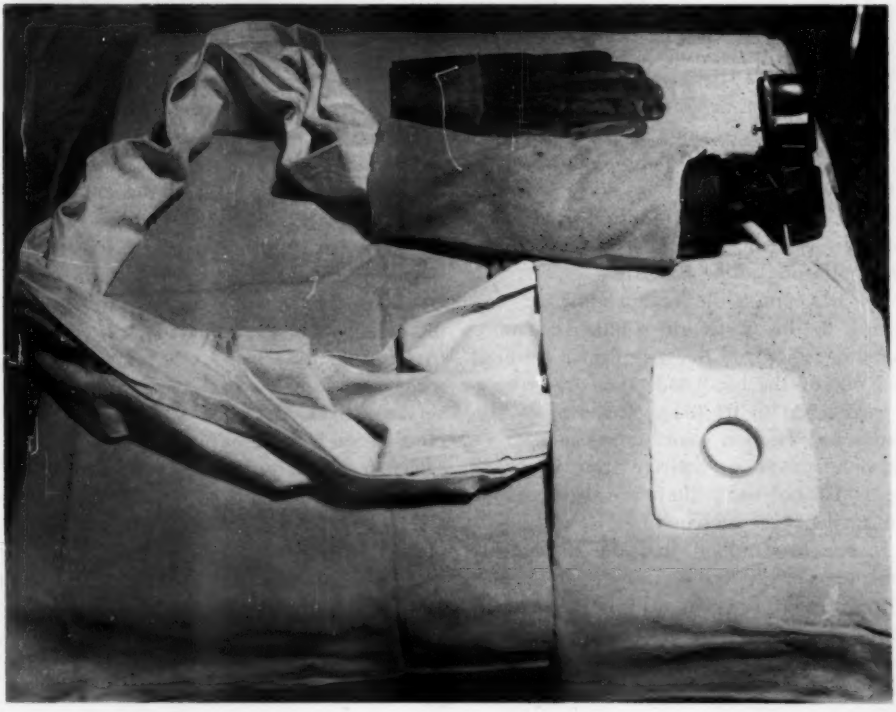

Fig. 2.—The binocular indirect ophthalmoscope of Schepens, detached from its headband, in use during operation. With this arrangement the instrument may also be used monocularly.

out the operation or of having it repeatedly placed and adjusted upon the head.

As is well known, the ophthalmoscope consists of a horizontal stereoscopic viewing element and a vertical barrel-shaped illuminating element—the lamp housing—these being attached to the headband.

To disconnect the ophthalmoscope, the wiring to the transformer plug is temporarily detached and the wire drawn through and out of the headband; then the wiring is reattached to its plug. Removal of the clamp and friction joint screws now frees the ophthalmoscope entirely from its headband. The accessory filters are also removed for further ease of handling.

It has been found that the instrument functions equally well optically in an upside-down position, whereby the now downward-pointing barrel-shaped lamp housing may be grasped and employed as a handle. The handle stays cool surprisingly long, and, when it does heat after prolonged use, it quickly cools again with the current off.

Measures to ensure sterility are comparable with those employed in the use of the direct ophthalmoscope in operations. A dental drape covers the wiring and lower portion of the handle, the remainder of which is enclosed in a sterile towel. The instrument is laid upon a pile of sterile towels to the side of which is a pile of gloves which are a half-size larger than the observer's customary size. The observer slips on a second glove and uses a new towel each time he picks up the instrument (Fig. 1).

The instrument may be used monocularly if the observer so desires by the simple maneuver of shifting the head to one or the other side.

There are obviously other ways in which the detached ophthalmoscope may be used at operation. For example, a sterile hemo-

stat may be employed to grasp the instrument. Alternatively, a stand with a sterile clasp can be used to hold the draped ophthalmoscope when not in use. Perhaps best of all would be a movable floor stand containing an adjustable arm to which the ophthalmoscope could be attached, to be used or swung out of the way as needed.

However, the method described has proved practical and useful in operations consisting of the scleral buckling procedures (Fig. 2) and the removal under direct vision of intraocular foreign bodies.

210 Angell St. (6).

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Annual Reviews

# Neuro-Ophthalmology

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The current articles on the optic nerve have been reviewed by Hollenhorst in the May, 1958, issue of the A. M. A. ARCHIVES OF OPHTHALMOLOGY.[1] However, I should like to mention a few conditions of optic nerve involvement with intracranial implications.

## The Optic Nerve

Friedman[2] reviews the literature regarding the etiology, pathology, and diagnosis of papilledema in patients who appear well in other respects. He believes that the papilledema is probably caused by increased intracranial pressure, possibly associated with venous thrombosis.

Papilledema in the absence of raised intracranial pressure is described by Roper-Hall.[3] This condition is to be found chiefly in various types of vascular affections, and it was suggested that the gradual reduction of nutrition and anoxia of the nerve might be sufficient to lead to edema without loss of function. Levatin[4] states that expanding lesions in the middle fossa may occlude the vaginal space about the optic nerves preventing papilledema, a condition found in glioma involving the intracranial optic nerves and optic chiasm. This is also the reason for absence of papilledema in pituitary adenomas and should therefore aid in differential diagnosis.

François, Verriest, and Baron[5] relate the occurrence of sudden loss of central vision with papilledema and papillitis, citing in detail seven cases with various conditions including arteriosclerosis, temporal arteritis, polyarteritis nodosa, Raynaud's disease, and polycythemia vera. They believe that the sudden occlusion of the blood supply or drainage, arterial or venous, disturbs metabolism to such an extent that edema and inflammation develop. Slower occlusion is compensated for and does not result in this condition. Joynt[6] speaks of the mechanism of the production of papilledema in the Guillain-Barré syndrome, suggesting cerebral edema rather than interference with cerebrospinal fluid absorption as the cause of increased intracranial pressure which results in papilledema.

Votockova[7] states that one may have difficulty in diagnosing and differentiating between pseudopapillitis and slowly developing papilledema, especially in the young who have great compensatory ability to withstand increased intracranial pressure and infection.

Pigasson, Garipuy, and Lazorthes[8] place great importance and diagnostic significance in the pulsation of the retinal vessels. They state that this pulsation is present in 95% of normal subjects and in cases of papilledema without increased intracranial pressure but is never found when there is an intracranial hypertension. They believe that this is an earlier and more consistent indication of increased intracranial pressure than papilledema.

Dreyer[9] differentiates between papilledema produced by increased intracranial pressure, such as an expansive tumor, brain swelling, and hydrocephalus, and papilledema of local involvement, such as physiological abnormalities, pseudoneuritis, drusen at the disc, and hyperemic disc: A third group includes post-traumatic arachnoiditis and aseptic sinus thrombosis.

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Porua and Carrion [10] report 15 cases of Foster Kennedy syndrome in patients with optochiasmal arachnoiditis.

Milosavljevic and Stankovic [11] distinguish the difference between early post-traumatic papilledema from vasomotor irritation with general cerebral concussion and late post-traumatic papilledema or choked disc from increased intracranial pressure. J. Wertheimer and P. Wertheimer [12] review 90 cases of papilledema with reduced visual acuity, visual field defects, and segmental or concentric constriction and conclude that they are of no localizing value.

Slade and Weekley [13] report a case of diastasis of the right optic nerve caused probably by an abnormal branch of the right internal carotid artery. Rucker [14] gives an interesting history of an investigation leading to the establishment of the proof of semidecussation of the optic nerves in man, the concept of which, as he states, originated with Sir Isaac Newton.

In a symposium on retrobulbar optic neuritis Geraud and Gayral [15] describe various affections and degenerations producing this condition. The affections are multiple sclerosis, neuromyelitis optica, syphilis, polyneuritis, and encephalitis. The degenerative conditions are known by the names of Friedreich, Dejerine-Sottas, Charcot-Marie, Merzbacher-Pelizaeus, and Pierre-Marie.

Shubova and Konchakova [16] discuss the significance of ocular symptoms in multiple sclerosis which were found in a series of 66 cases. François and Verriest [17] describe retrochiasmal neuritis in multiple sclerosis and cite two cases in which optic tract involvement produced central homonymous visual field defects.

Calvert, Claux, and Lo [18] found only 4 cases of ethmoid infection in 31 patients with retrobulbar optic neuritis. Lazorthes [19] believes that there is a vasomotor factor in retrobulbar neuritis which produces edema. This can be treated by decompression and by vasodilatation with drugs or by operations upon the sympathetic system to improve the blood supply.

Lazorthes, Anduze-Acher, and Espagno [20] report 17 cases of transfrontal exploration, in 11 of which the optic canal was trephined. The optic nerve was found to be pale but not swollen, a condition which probably occurs later and results in pressure damage. Riser, Garrigues, Rascol, and St. Marc [21] state that compression damage to the optic nerve from expanding lesions should not be termed neuritis, as inflammation is not present. Riser, Lazorthes, Geraud, Gagral, and Anduze-Acher [22] suggest early complete sympathectomy in selected cases of toxic-infectious optic neuritis.

Blagojevic and Arambasic [23] report 250 cases of optic nerve involvement with edema or atrophy in patients with tuberculous meningitis. Interstitial neuritis with occasional chiasmal involvement and arachnoiditis were constant findings.

Zahradnicek and Dolenek [24] found from a total of 30,720 hospitalized patients, 25 children with optic atrophy from expanding intracranial lesions, congenital anomalies of the central nervous system, syphilis, and trauma.

Shaw and Duncan [25] discuss the coexistence of diabetes mellitus and optic atrophy in members of a family and mention this condition as appearing in three other unrelated families.

Meningioma invading the optic nerve with intraocular extension was cited in a boy, aged 3 years, by Martin and Schofield.[26]

Fowler and Watson [27] discuss gliomas of the optic pathways in childhood. The ocular symptoms are proptosis, papilledema, and decreased visual acuity. The intracranial symptoms aside from radiologic evidence, such as erosion of the sella and enlargement of the optic foramen, are due to increased intracranial pressure. Liss and Wolter [28] describe the histopathology of a case of optic nerve oligodendroglioma.

Chamlin,[29] in his discussion of visual field defects from optic nerve compression by mass lesions, states that central scotomata

per se are rare and of no diagnostic value. Compression of the nerve causes peripheral field defects which may include central loss. Contralateral temporal defects result from mass lesions. There is no selectivity of certain axons demonstrable from pressure damage.

Colas, Collet, and Chevannes [30] discuss the occurrence of optic nerve lesions found in 16 of 3000 cases of head trauma. The optic nerve may become damaged by contusion, interference with the blood supply, and compression hemorrhage in the nerve sheath. Surgery did not result in improved vision, and patients seemed to do as well without surgery.

Hughes [31] describes the blood supply to the optic nerve and chiasm and discusses its clinical significance. He concludes that the stretching and kinking of the nerve with compression and not the involvement of the blood supply accounts for central scotoma.

### Orbit and Middle Cranial Fossa

The diagnostic value of orbital angiography is demonstrated by Krayenbuhl,[32] who states that its chief value is in the demonstration of pathological vascularization of space-occupying lesions as well as in the displacement of the ophthalmic artery and its branches. Langmaid and Daws [33] present two cases of congenital bone defects in the orbital wall in von Recklinghausen's disease producing pulsating exophthalmos revealed by cerebral angiography.

Scott [34] discusses the ocular aspects of endocrine exophthalmos with differential diagnosis, especially those cases remaining unilateral with loss of visual field. Discussing progressive exophthalmos in lesions of the middle fossa, Wanke and Graf [35] found, instead of the usual sphenoidal meningioma, four cases of serous arachnoiditis with reduction of the lumen of the optic canal and superior orbital fissure.

Buxeda [36] describes a case of chiasmal optic neuritis with involvement of the visual fields of both eyes showing incongruous scotomata.

Nieberling [37] describes ophthalmological findings in optochiasmatic arachnoiditis in 16 cases with visual field loss, exophthalmos, and muscle disturbances. Schweitzer and Espilidora [38] report 22 cases in which they found pallor of the disc with bizarre field loss to be the only constant diagnostic features.

Moi [39] in a study of 50 patients endeavors to find the reasons for misdiagnosis of tumors near the optic chiasm, which are often thought to be retrobulbar neuritis or optic atrophy of undetermined origin. He states that intrasellar tumors show temporal hemianopia with defects starting in the upper temporal quadrants, with preserved vision. Unilateral visual loss and visual field defects beginning in the lower temporal quadrant are found in suprasellar tumors. Encephalography is an important aid in this examination.

Jefferson, Pollak, and Yates [40] discuss the method by which neighboring gliomas reach the optic nerve and chiasm and the nature of these invasive tumors.

Kearns and Rucker [41] describe the occasional arcuate defect in the visual fields without bitemporal loss in cases of chromophobe adenoma. They state that x-ray of the middle fossa and endocrine examination are helpful. Morgensen [42] gives a statistical review of chromophobe adenoma of the pituitary gland. Indications for operation are enlargement of the sella turcica and restriction of visual fields. C. W. Rand and R. W. Rand,[43] reviewing 100 patients, believe that, unless there is rapid loss of field or of vision, x-ray should be tried. They state that cystic tumors respond poorly to x-ray. Chamlin [44] discusses the visual field changes following x-ray treatment of pituitary tumors. He believes that one should allow at least four to six months after treatment before judging the results and two to three years before determining the final total benefit. He states that there usually is an excellent response to radiotherapy in early and noncystic tumors. He recommends frequent visual examination during

the course of the treatment. Buys and Kearns Jr.[45] regard the high dose of irradiation required to treat pituitary involvement properly as possibly damaging to adjacent visual structures. They recommend thorough consideration before the patient is subjected to this treatment.

Steiner[46] states that a patient with a lesion in the middle fossa is usually seen first by an ophthalmologist, as the symptoms are those of visual impairment. He recites the various difficulties encountered in diagnosis.

In discussing Rathke's pouch tumors, Northfield[47] gives as the presenting symptoms impairment of vision and diplopia. Headache, vomiting, dementia, and epilepsy also may be present. Other ocular symptoms are visual field defects, papilledema, optic atrophy, and visual hallucinations consisting of flashes of light which may be colored: In his series, he reports three cases of organized hallucinations. Rintelen and Lenenberger[48] give the pathology and clinical findings with differential diagnosis of craniopharyngioma, stressing the importance of accurate visual field studies.

Grant and Hedges[49] review the ocular changes in 30 patients with meningioma of the tuberculum sellae and make a plea for earlier diagnosis and treatment. Central hemianopic visual field loss may be the only presenting symptom. Newell and Beaman,[50] in a review of 145 patients, present verified meningiomas of the tuberculum sellae which produce bilateral optic atrophy, meningiomas of the sphenoidal ridge with unilateral optic atrophy and proptosis, and meningiomas of the olfactory groove which show visual impairment infrequently until the condition is advanced.

Masson and Mansuy[51] discuss sphenoccipital chordomas and present two cases. They describe these tumors, with a dense fibrous capsule, as benign and noninvasive, damaging neighboring structures by compression.

Glees and Zielinski[52] discuss the occurrence of bitemporal central and paracentral scotoma in various pathological processes in the region of the sella turcica from which the location but not the type of lesion can be determined from the ocular symptoms which are found early and are of primary importance. Eleven cases are reported.

Fourcade, Vaiehe, and Lavant[53] tell of retinitis pigmentosa and the hypophyseal syndrome and describe a case with hypoglycemia, polyuria, flat glucose-tolerance curve, and inhibited secondary sexual characteristics, with pigmentary degeneration of the retina.

## Vascular Affections of the Visual System

The use of arteriograms for diagnostic value in observing the state of vascular conditions has brought renewed interest in the blood supply to the visual system. Finkemeyer[54] presents three cases demonstrating anastomoses between the internal and external carotid arteries with occlusion of the internal carotid and describes anastomoses between branches of the temporal and ophthalmic arteries. Lehrer[55] demonstrates with arteriography anastomoses between cerebral arteries and the ophthalmic and external carotid arteries.

François, Neetens, and Collette[56] continue their excellent description of the vascularization of the primary optic pathways. They state that the absence of hemianopia after ligation of the anterior choroidal artery is explained by the anastomosis with the posterior communicating artery. Dubois-Poulsen and Magis[57] usually found upon ligating the anterior choroidal artery sufficient collateral circulation to prevent visual disturbances. The entire syndrome of the anterior choroidal artery, consisting of hemiplegia, hemianesthesia, and homonymous hemianopia, may therefore not occur.

Alexander[58] describes vascular lesions affecting the visual pathways with special reference to those in the region of the temporal isthmus which produce contralateral hemianopia, aphasia, agraphia, alexia, and frequently hemiplegia. Symptoms resulting from lesions of Areas 18 and 19

(Brodmann) are discussed. These are areas of visual recognition and revisualization.

In an article on the regulation of the cerebral circulation, Brain [59] discusses the usual early symptoms produced by atheroma of the internal carotid artery. Transitory amblyopia is frequently found to be due to a temporary fall in the blood pressure in the ophthalmic artery.

Sastrasin [60] gives a statistical review of 65 patients with carotid thrombosis, 19 of whom had visual disturbances. Chrast and Gottwald [61] believe that the symptoms of carotid thrombosis are not pathognomonic. The symptoms are chiefly loss of vision and eye muscle paralysis.

Ricci and Werner [62] discuss the chiasmal syndrome and present two cases in which the internal carotid arteries have compressed the terminal optic nerves or optic chiasm.

Van Allen, Blodi, and Brintnall [63] explain a method of determining retinal arterial pressure with ophthalmodynometer. This is a proven aid in determining vascular occlusion, which is indicated by lowered pressure.

Symonds and Mackenzine [64] discuss bilateral loss of vision from occipital lobe infarction seen in 33 postmortem examination and 25 unverified histories. The loss of vision was usually sudden and accompanied by vertigo. Psychic areas with their symptoms were occasionally involved. Emboli were most frequently found in the calcarine artery; thrombus, in the basilar and vertebral arteries.

Alfano, Fabritius, and Garland [65] discuss visual loss following mitral commissurotomy for mitral stenosis in a report of two cases with references to others who had obstruction, either thrombus or embolus, in the posterior cerebral arteries resulting in loss of vision and visual fields.

Offret and Godde-Jolly [66] describe aneurysms of the ophthalmic artery, one at its origin from the internal carotid, the other along its course. Symptoms depend upon location. White Jr. and Foltz [67] review the literature of optic atrophy in relation to aneurysm of the carotid artery. The cause of many progressive unexplained optic atrophies can be revealed by arteriography. Baumann and Bucy [68] believe that surgical intervention is important early in the course, obviously before rupture.

Alfano and Reese [69] present a lucid and terse but comprehensive description of types of angioma with symptoms and diagnosis. Dimsdale [70] discusses the symptoms, dependent on the location of the lesion, produced by cerebral angiomas.

Taylor [71] discusses the varieties of cavernous sinus thrombosis with their symptoms and presents two cases. Because of the possibility of penicillin resistance, he recommends that antibiotics be given upon diagnosis in order to save valuable time.

Smith, Kearns, and Sayre [72] believe that subarachnoid hemorrhage accompanied by preretinal or optic nerve sheath hemorrhage is probably due to increased venous pressure secondary to sudden increased intracranial pressure and is not the result of forward extension of blood along the subarachnoid space of the optic nerve from the cranium.

Chrast [73] does not believe that late papilledema is caused by intracranial hypertension in subarachnoid hemorrhage. He reports seven patients who developed edema of the papilla 10 days to 6 weeks after hemorrhage. In their study of subdural hematoma Hollenhorst, Stein, Keith, and MacCarthy [74] found ocular symptoms to be the most constant, occurring in about 60% of the cases. The chief symptoms were retinal hemorrhage and, less frequently, extraocular muscular palsies and papilledema. Echlin, Sordillo, and Garvey [75] found 300 subdural hematomas among 30,000 head injuries. They suggest that the time of operation should depend upon the symptoms.

### Involvement of Visual Psychic Areas

Schnele [76] describes concise and readily adaptable clinical tests for determining visual impairment in aphasia of various types. Ettlinger, Warrington, and Zangwill,[77] in their study of visual spatial agnosia, dis-

cuss theories which may possibly explain the restricted fields of visual attention with spatial loss.

In a clinical study of 100 aphasic patients Brown and Simonson [78] found that defects in reading were often associated with homonymous hemianopia usually from a small lesion most frequently in the posterior temporal, parietal, and anterior occipital lobes. Warrington and Zangwill [79] describe a syndrome of word-blindness (alexia) with the inability to read which may be accompanied by right homonymous hemianopsia, loss of color vision, and dysphasia in which following eye movements often show gross abnormalities owing to disordered perception.

Dessoff [80] cites a case with reading difficulties which are found usually in lesions of the optic radiations with paracentral homonymous scotomata. If the scotoma is on the right, there is difficulty in reading; if on the left, there is difficulty in finding the next line. In this condition optokinetic tests with the rotating drum are of diagnostic aid (Lyle [81]).

Bergman [82] discusses cerebral blindness and analyzes 12 patients with reference to the electroencephalogram pattern. The chief symptoms are bilateral blindness to light perception, retention of pupillary light reflexes, denial of blindness (Anton's syndrome), absence of optokinetic nystagmus, and other disturbances of organic and psychic nature.

Sokolic and Gvozdanovic [83] cite a case of occipital parietal porencephaly, possibly of traumatic origin, with incongruous homonymous hemianopia, sparing of the macula, and unawareness of field loss. Fink [84] tells of a patient with loss of vision, hemiparesis, and delirium with denial of blindness after cerebral angiography.

Gerstman [85] explains the syndrome bearing his name with symptoms of finger agnosia, agraphia, acalcula, right-left disorientation, and disorientation in personal space.

### Lesions of Optic Tract and Radiations

Lenfelder [86] describes various syndromes associated with visual field changes from lesions along the course of the visual system. Sokolowski and Segal [87] cite a patient with mechanical trauma to the optic tract which produced symmetric homonymous hemianopia with absence of macular vision. Wernicke's syndrome was found in the involved field.

Several authors describe the effect upon the visual fields of temporal lobe surgery. Falconer and Wilson [88] studied visual field changes in 50 patients following anterior temporal lobectomy and concluded that the upper quadrantanopia is congruous. Murphy,[89] in a study of eight patients, found no field defect if less than 60 mm. of the temporal tip was removed, and a superior contralateral homonymous quadrantanopia was produced with removal of 55 to 90 mm. He found that hemianopia may occur if more than 80 mm. is resected. This study shows that the forward loop does not extend to the tip of the temporal lobe. On the other hand, Björk and Kugelberg [90] found the visual radiation fibers extending to the anterior tip of the temporal lobe in a study of 26 patients, and after amputation of this portion they found upper contralateral quadrantanopia.

### Visual Field Studies

Schlaegel Jr.[91] discusses the significance of the spiral visual field. Although he believes it to be functional, it may be induced by fatigue from organic intracranial lesions. Toussaint [92] describes the characteristic field defect of hysterical amblyopia and states that there may also be an element of organic disease upon which there is functional expansion.

Magis [93] presents an extensive monograph on visual fields in which he discusses the theory and method of visual field testing and the errors of perimetry. Alexander [94] discusses the diagnostic value of color fields. He uses 2 mm. targets of red, which he be-

lieves give more consistent results than the small white target.

### Ocular Motility

Breinin [95] from his studies of electromyography describes various supranuclear and internuclear reactions which demonstrate the behavior of the extraocular muscles, which he states is similar to that of other skeletal muscles but is dominated and modified by the visual system. In another article he [96] discusses the pattern of electromyography in a number of neuro-ophthalmological conditions, diabetic paralysis, aberrant oculomotor regenerations, myasthenia gravis, muscle dystrophy, thyroid paralysis, Mobius syndrome, and various types of paretic strabismus.

Rodriquez Barrios, Bottinelli, Maslenekov, Acevedo-de-Mendilaharsu, Mendilaharsu, Medoc, and Garcia [97] present a study of intracranial trauma and vascular accident by labyrinth stimulation with observations of reflex ocular movements such as conjugate deviation and nystagmus. They believe that absence of response (probably indicating brain stem lesion) is a fatal symptom. Cogan [98] makes some objective and subjective observations on the vestibulo-ocular system. He states that, although labyrinthine control is subordinated to voluntary and reflex mechanism in man, it is of vital importance in adjusting and stabilizing eye movements.

Bender, Postel, and Krieger,[99] in a review of concepts regarding the presence of an occipital oculomotor field, state a belief that the occipital cortex plays a part in oculogyric control by way of the visual reflexes. Fisher [100] discusses the types of command and voluntary eye movements produced by a lesion in the nondominant hemisphere which can be executed but not maintained. Urrets-Zavalia and Remonda [101] review the literature concerning oculomotor apraxia and discuss lesions of the frontomesencephalic and occipitomesencephalic tracts. Involvement of the latter results in loss of fusional movements, convergence, and pupil light reflexes. Following and fixing movements are also impaired.

Witzel [102] discusses various types of conjugate paralysis and presents a case of bilateral conjugate paralysis with absence of command, following, and random movements while the vertical movements and convergence remain present. He suggests a possible pontine center for control of lateral movements.

Milosavljevic [103] discusses various causes and forms of progressive ophthalmoplegia not only as results of isolated muscle changes but also as signs of previous encephalitis. Kirschbaum and Holland [104] suggest conditions which produce chronic progressive nuclear paralysis but state that the majority of cases have a myodegenerative rather than a nuclear pathogenesis. Bonduelle, Boygues, and Puech,[105] in a discussion of persistent ophthalmoplegia preceding peripheral myasthenic syndrome, suggest that the causes may be superior poliomyelitis and progressive nuclear ophthalmoplegia with periodic ocular paralysis.

Fisher [106] describes an unusual variant of acute idiopathic polyneuritis with the symptoms of total external ophthalmoplegia, ataxia, and areflexia and suggests its relation to the Guillain-Barré syndrome. Smith and Walsh [107] discuss this condition and report several cases. They found downward eye movements usually preserved, with an associated seventh nerve palsy.

Priggert [108] discusses paralysis of the ocular muscles in herpes zoster ophthalmicus, which he believes is produced by passage of virus to nuclei of the nerves of the ocular muscles.

Troupp, Koskinen, and Björkesten [109] advocate early trapping of an aneurysm which has produced oculomotor paralysis. Eight cases are reported. Schachat, Wallace, Palmer, and Slater [110] review ophthalmologic findings in children with cerebral palsy. They found twice as many ocular defects requiring attention in children with a spastic type as in those with an athetoid type. Because of the amount of ophthalmo-

logical involvement, the need for early and complete examination and treatment is evident. A routine screening should be made of every child with cerebral palsy.

Clinical lesions involving the oculomotor nerve are discussed by Alfano [111] with cause, location, and differential diagnosis. Causes and types of third nerve degeneration and regeneration are described by Walsh,[112] and electromyographic studies are discussed, with diagnosis and prognosis, in a variety of conditions.

With increasing prevalence or with more interest and diagnostic acumen, various types of paralysis of the oculogyric system are being reported in the diabetic. Dreyfus, Hakim, and Adams [113] discuss this condition and state that the pathogenicity is not entirely understood but that they believe, on the basis of postmortem studies, that the probable cause is occlusion of nutrient vessels to the nerve. Sullivan [114] discusses the motor and sensory nerve affections due to diabetes, implicating the ocular muscles and sensory nerves to eye and adnexa.

Lowenstein and Lowenfeld [115] continue the study of electronic pupilography, giving further information regarding pupil reaction in lesions of the pupillomotor system and brain stem in which one is able to determine clinical localization and diagnosis. Lazorthes, Pigassons, and Gaubert [116] describe the course of the fine and coarse fibers in the oculomotor nerve. The fine fibers serving the intrinsic muscles of the eye, being on the periphery, are vulnerable as they pass the posterior clinoid process and the cerebellar tentorial rim. This is frequently the cause of dilated pupils by compression of the nerve in these areas. Miani [117] reports a case with loss of light reflex and retention of consensual reflex, partial optic atrophy, and loss of temporal field which supports the view that pupillomotor fibers are found only in the nasal sector of the optic nerve.

In the section of the *Survey of Ophthalmology*, devoted to classics of ophthalmology, Lebensohn presents an interesting article by Adie [118] describing the syndrome which bears his name.

Deutsch [119] discusses monocular internal ophthalmoplegia and reports three cases with diagnosis and localization. Pietruschka and Stump [120] report a patient with neurosyphilis who showed combined paradoxical pupillary movements and discuss causes for this phenomenon.

Bedrossian [121] discusses bilateral abducens paralysis simulating divergence paralysis. The diagnosis is made by finding an increase in diplopia in the field of action of the paralyzed muscle: With divergence paralysis the diplopia increases with the distance but the angle of deviation remains the same along the circle of the arc. Progressive bilateral abducens paralysis resulting from atheromatous changes in the carotid artery within the cavernous sinus is reported by Bonnet and Bonnet.[122] The associated paralysis of the abducens nerve and the contralateral facial nerve, probably produced by herpetic virus, is reported by Montresor.[123]

### Nystagmus

Gorman, Cogan, and Gellis [124] present an apparatus to determine the visual acuity of infants on the basis of optokinetic nystagmus reaction. Tichy [125] describes optokinetic nystagmus as a cerebral reflex developing in the child during the third to fourth month after birth. Abnormality of this reflex, the author believes, may be caused by both frontal and occipital affections. He believes this test to be a valuable lateralization aid. Tschiassny [126] describes the reaction of perrotation nystagmus in the ballet dancer, the pigeon, and the blind person and applies this knowledge to differentiate between organic and psychic or functional blindness.

Sala [127] finds loss of the rapid phase of optokinetic nystagmus due to lesions in the posterior portion of the corpus callosum and the bulbopontine region. He finds loss of the slow phase with upward movement of the eyes in lesions of the superior quad-

rigemina. Enoksson [128] concludes from the study of a large series that optokinetic nystagmus is of little value in localizing brain lesions.

Vaernet,[129] in testing the caloric vestibular reactions in patients with transtentorial herniation of the brain stem, found that affections in this area produce dissociation of eye movements without the compensatory return, the quick movements, of the induced nystagmus.

Nathanson, Bergman, and Anderson [130] discuss the oculocephalic reflex (Doll phenomenon) and the caloric tests, which they believe are better than the corneal and pupillary reflexes in determining the degree of unconsciousness. These tests also serve to diagnose and localize the lesion. If these tests are negative or if disjunctive ocular movements are induced, midbrain or pontine lesions are likely to be present.

Larsen [131] describes a case of see-saw nystagmus produced by a tumor of the brain stem. Other symptoms were motor instability and increased intracranial pressure. Bonnefoy [132] reports a case of a lesion in the posterior inferior wall of the third ventricle which produced rhythmic retraction of the eyeballs and paralysis of upyard eye movements.

Magistretti [133] discusses the Parinaud syndrome in neuromuscular disease induced by mesencephalic supranuclear lesions.

### Sensory Affections

Toussaint [134] discusses Raeder's paratrigeminal syndrome and presents two cases with symptoms of ptosis, miosis, and hyperesthesia in the ophthalmic nerve distribution with impaired corneal sensitivity. Minton [135] presents a patient with herpes zoster ophthalmicus following virus encephalitis with contralateral anesthesia and hemiplegia.

The operation of choice for tic douloureux of the ophthalmic division, according to Rubin,[136] is peripheral neurectomy of the main branches of the ophthalmic division excepting the lacrimal nerve in order to spare, to some extent, the unpleasant effects and occasionally impaired vision due to corneal involvement.

Ryan [137] states that a small but important number of headaches are of ocular origin. This chapter on ophthalmologic causes of head pain is contributed by Drews. Almeida [138] describes types of head pain.

In regard to the facial nerve as it affects ophthalmology, Friedman [139] describes the Marin-Amat syndrome, in which the eye is closed with movement of the mouth, which is an inverse phenomenon of the Marcus Gunn syndrome, in which there is contracture of facial musculature on closure of the eye.

### Sympathetic System

There are several articles in reference to the sympathetic nervous system. Bonnet [140] gives the history of its discovery by Pourfour du Petit and its recognition and description by Claude Bernard and Horner. Palumbo,[141] citing 45 operations upon the upper thoracic sympathetic chain without the occurrence of Horner's syndrome, believes that the preganglionic neurons pass from the eighth cervical and first and second thoracic segments by a separate route to the superior portion of the stellate ganglion and not, as usually described, by the white ramus communicans to the superior thoracic and cervical ganglia. Dejean, Viallefont, and Boudet [142] state that stimulation of the superior cervical ganglion in man causes a fall in retinal arterial pressure in the ipsilateral eye with no effect upon the caliber of the vessels or intraocular pressure. Stimulation of the stellate ganglion produces bilateral fall in arterial pressure.

Bray, Carter, and Taveras [143] discuss brain stem tumors in children. They state that an expanding tumor in the brain stem implicates oculogyric structures, producing eye and muscle incoordination or paralytic strabismus along with disturbances of gait and dysarthria. Ultimately intracranial pressure is increased from closure of the ventricular system. Busch [144] from a study

of eight patients with pinealomas finds the earliest symptoms to be increased intracranial pressure with papilledema, anisocoria, diplopia with third and fourth nerve involvement, and paralysis of upward gaze. Bitemporal hemianopia due to dilation of the optic recess and one case of homonymous hemianopia were seen.

### Cerebral Influence of Intraocular Pressure

The interesting discussion of cerebral control of intraocular pressure continues. Cavka [145] speaks of the frontal and diencephalic regulating centers of intraocular pressure. He suggests that glaucoma results from inflammation or intoxication in these areas. Gloster and Greaves [146] suggest in their study that the fall of intraocular pressure is due to reduction of the blood supply which is regulated by diencephalic centers. Waisfeld and Katzman [147] state that increased intraocular pressure was found in the eye on the side opposite vascular, traumatic, and inflammatory cortical lesions, leading them to assume that an asymmetrical contralateral pressure increase results from reflexes from cortical lesions. Brand [148] submits material suggesting the presence of a cerebral center which influences or controls intraocular pressure.

Two articles have been found on phacomatoses. Wagner [149] describes tuberous cerebral sclerosis and reports a case of glial-cell tumors in the brain and retina with tumors of the kidney, thyroid, lymph nodes, and osteitis deformans. Stokes [150] discusses the ocular manifestations of the Sturge-Weber syndrome with its complications which produce intracranial hemorrhage, epileptiform fits, palsies, and visual field loss.

Of general neuro-ophthalmologic interest is the presentation of Mooney,[151] who discusses conditions of interest and concern to both ophthalmologists and neurologists. He presents a number of cases to typify the various conditions and emphasize the importance of liaison between the two specialties. Uihlein [152] describes the usual neurologic conditions producing acute visual failure, such as tumors, vascular lesions and inflammations in the middle fossa, hydrocephalus, pseudotumor cerebri, and injury.

Kurz [153] has written an excellent book on neuro-ophthalmological diagnosis with a historical introduction. Polyak [154] has presented us with the tremendous work of a lifetime on the vertebrate visual system which follows his book on the retina. Ancient and modern history of investigation is dealt with. This is followed by an exposition of the anatomy and histology of the visual pathways and centers, with investigation of structure and function. Embryology and comparative anatomy are included in the final part of this exceptional study.

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# Correspondence

## OCULAR MANIFESTATIONS OF RILEY-DAY SYNDROME: FAMILIAL AUTONOMIC DYSFUNCTION

*To the Editor:*—The article by Liebman on ocular manifestations of Riley-Day syndrome in the November, 1956, issue of the ARCHIVES, page 719, presents descriptions and illustrations of a condition we see much of in India. The condition is lack of vitamin A, which leads to more blindness among children in the parts of India in which I have worked than any other condition.

The dryness of the conjunctival sac, the lack of tears, is only part of a process in which the mucous membranes of the whole body lose their mucous quality and become squamous. The cornea may be dull, epithelium-thick or deeper, or may become like white blotting paper in appearance and consistency. The mystery of keratomalacia is the tremendously toxic action on the cornea. How can such a strong and beautiful organ, through which only Greishaber's needles will go easily, become so soft so quickly?

Would that Dr. Cogan, pathologist, could have obtained in the fatal case described sections of the intestine and of the lacrymal gland that was not functioning. Dr. Cogan's statement that "no goblet cells are seen in the conjunctiva, but this may not be abnormal" must be wrong. "No goblet cells" in the conjunctiva is, I am sure, of tremendous importance clinically and cannot under any circumstances be anything but abnormal.

It is interesting that in vitamin A deficiency one eye may develop keratomalacia in the center which then extends out while the other eye may have just a deepening degeneration of the cornea following on an exposure keratitis, which is in itself a malnutrition of the cornea from lack of the moisture from winking, accentuated by lack of tears themselves, the seriousness of the condition accentuated greatly by vitamin A deficiency.

In some debilitating conditions of infants and children and also in adults the eyes do not close, and in conditions where the eyes do close and perhaps are not opened, the patient keeping the lids even tightly closed, vitamin A deficiency must be anticipated and protective injections given. The continuation of a diarrhea is of very great importance, for the changes in the epithelium of the intestinal tract prevent the absorption of vitamin A, making a vicious cycle.

I have heard from ophthalmologists in America that they have not seen a patient with vitamin A deficiency in all of their lives. Such an article as Liebman's, where outstanding illustrations of vitamin A deficiency have apparently been mistaken for ocular symptoms of Riley-Day syndrome, demonstrates the need for Western oculists and pediatricians to alert themselves to the possibilities of vitamin A deficiency, chronic and acute.

Has the condition described by Liebman something to do with Riley-Day familial dysautonomia, or is it the result of a frank malnutrition headed off by vitamin A deficiency?

Dr. Rambo's letter (first published in the January, 1958, issue of the ARCHIVES, p. 147) is being reprinted here so that it may be reread in relation to the accompanying replies by Drs. Berenberg and Liebman.

What was the diet of the children at home and at the hospital? Was vitamin A therapy tried out either at home or in the hospital? Was there involvement of the skin?

In these conditions where there might possibly be a vitamin A deficiency it is very necessary not to take any chances. It is most necessary to give 100,000 units of vitamin A intramuscularly, daily, in severe debilitating conditions, especially if there is any suggestion of ocular symptoms of dryness, or lack-luster, of conjunctiva or cornea. It would be tragic to follow Dr. Liebman's suggestion in such conditions and give a "protective ointment, instilled at night," some test for vitamin A deficiency being positive or negative, as the case may be.

One of the most satisfying and startling responses of the body to treatment in all of medicine is the response of the fish-scale or finger-nail appearing cornea of prekeratomalacia to an injection of vitamin A. Within fourteen hours, if caught at the right time, the cornea has regained its natural shine and clearness, to fill the surgeon with awe and gladness at the transformation. Much more vitamin A must be given over sometimes a long time, together with the establishment of an adequate diet that is absorbed, but the initial response is most gratifying. Let us not let our little, or larger, patients ever get so low in such an important ingredient of living cells.

VICTOR C. RAMBO, M.D.
Christian Hospital
Mungeli, Dist. Bilaspur, M. P., India

*To the Editor:*—Dr. Sumner Liebman has asked me to comment on the letter from Dr. Victor C. Rambo relating to Dr. Liebman's article on ocular manifestations of the Riley-Day syndrome.

It is quite understandable that Dr. Rambo should be impressed with the similarity between the ocular manifestations in familial dysautonomia as described by Dr. Liebman and those present in vitamin A deficiency. As the physician concerned with the care of a child described in Dr. Liebman's article, I can assure you that our immediate attention was drawn to the possibility of vitamin A deficiency, as soon as the ocular manifestations became apparent. The child had received 7000 units of vitamin A since birth as part of a multivitamin preparation. This dose had been increased at the time of initial ocular manifestations to 75,000 units of vitamin A intramuscularly daily for a long period of time without any effect except for progressive worsening of the ocular change. Prior to the time that vitamin A was administered parenterally, studies were carried out which showed high-normal levels for vitamin A and carotinoids in the patient's plasma, on two separate occasions. In addition, a vitamin A tolerance and absorption curve showed normal uptake of vitamin A from the aqueous multivitamin solution which the child had received.

I am in no position to make any comment regarding Dr. Rambo's statement for the "need for Western oculists and pediatricians to alert themselves to the possibilities of vitamin A deficiency, chronic and acute," but am pleased that his misinterpretation of the findings in Dr. Liebman's report emphasizes the need for recognition of the ocular manifestations of familial dysautonomia, from which the patient described certainly suffered.

WILLIAM BERENBERG, M.D.
Assistant Clinical Professor of Pediatrics,
Harvard Medical School, Boston 15.

*To the Editor:*—I think it is obvious from the text of my paper that vitamin A deficiency was seriously considered as a possible cause of the keratopathy in the patient which I reported as Case 1. Dr. Cogan's clinical and pathologic impression was vitamin A deficiency. It was Dr. Berenberg's discovery that the child had Riley-Day syndrome rather than avitaminosis which stimulated me to make my report. Since the medical evaluation of the patient as a whole is obviously vitally important to the argument, I have asked Dr. Berenberg to comment on Dr. Rambo's letter.

At my request, the Department of Pathology at the Massachusetts General Hospital recently reviewed the autopsy material in this case. Dr. William Thurlbeck, Pathologist, reports as follows:

"Microscopically, there was no evidence of squamous metaplasia of the bronchi, renal pelves, or the intestine, despite multiple sections. The pancreas was noted as normal grossly, but no sections of this organ were available. The lacrimal glands were not examined. . . . I doubt that this is a case of vitamin A deficiency on the basis of the autopsy findings."

Dr. Berenberg and I have maintained continued interest in the possible relationship between vitamin A and Riley-Day syndrome. The fasting blood vitamin A levels and vitamin A-absorption curves are well into normal ranges. One might postulate an inability on the part of the tissues to utilize this circulating blood vitamin A. However, if this were the fact, the administration of massive doses of viamin A (as urged by Dr. Rambo) would hardly solve the problem and, to date, clinically has been quite ineffective.

SUMNER D. LIEBMAN, M.D.
115 Bay State Road, Boston 15.

# Obituaries

## LAWRENCE T. POST, M.D.
### 1887-1958

Dr. Lawrence T. Post, son, brother and father of ophthalmologists, died on May 13, 1958, in St. Louis, after a long and distressing illness that he bore with great fortitude and dogged determination.

He was born in St. Louis on Dec. 25, 1887, the second son of Martin Hayward Post, M.D., eminent American ophthalmologist and President of the American Ophthalmological Society in 1915. His mother, Mary Lawrence Tyler, came from a distinguished family of Louisville, Ky. His grandfather, Truman M. Post, was the first Congregational minister to be located in St. Louis.

After attending local schools, particularly Smith Academy, he entered Yale University and graduated with the B.A. degree in 1909. He then entered The Johns Hopkins University Medical School and graduated with the M.D. degree in 1913. Here he came under the influence of those remarkable physicians and

LAWRENCE T. POST, M.D.
1887-1958

teachers William S. Halstead, Harvey Cushing, and William H. Welch. He was a popular member of that gay and lively undergraduate organization, the Pithotomy Club, which is an indication of his joviality, high spirits, and sense of humor which he bore with him all of his life, to the delight of his innumerable friends and devoted colleagues.

He served as surgical intern in the South Baltimore E. E. N. T. Hospital 1914-1915 and became associated with James Bordley Jr. in the practice of

ophthalmology. He spent three months in the fall of 1914 in the study of ocular pathology under the direction of Frederick H. Verhoeff, whose influence as a teacher persisted throughout life.

Following the death of his father in 1915, Dr. Post returned home and became associated with Drs. A. E. Ewing, W. E. Shahan, and his brother, Hayward Post Jr., in the practice of ophthalmology. The close association with his brother throughout his life was a splendid and inspiring thing.

In 1924 he married Bernice Lightner. Three children, Lawrence Tyler Jr., Stephen Lightner, and Robert Henshaw Post, were the fruit of this union. The upbringing of these fine sons reflects the devotion and mutual love of their parents and the peace of a happy home. Lawrence T. Post Jr., M.D. (Washington University) followed in his father's footsteps and is an established ophthalmologist in St. Louis. Stephen L. Post, M.D. (Columbia) is a psychiatrist. Robert is a medical student (Cornell).

Shortly after his return from Baltimore in 1915, Lawrence Post joined the group of General Hospital No. 21—the Washington University Unit which served in France. In 1917 as Major Post M. C., U. S. A. R., he served as Surgical Director, American Mobile Hospital No. 4, A. E. F., and soon was promoted to Lieutenant Colonel, and following World War I served in the Reserves until 1932. He maintained his interest in military ophthalmology for many years. He was a co-author of the ophthalmological and otolaryngological military surgical manuals, most useful to the military doctor. He was a member of the Ophthalmological Committee of National Defense, the National Research Council for the Armed Forces, and in 1941 a Consultant to the Administration Board of the National Research Council. Following World War II he served the Medical Department of the Veterans Administration from 1946 to July, 1951.

He excelled as a teacher, a position he loved. Shortly after his return from Baltimore to enter practice he joined the Eye Department of Washington University and worked through the ranks to the position of Professor of Clinical Ophthalmology and Head of the Department, Washington University, 1933-1953. He was chiefly responsible for the development of his department into one of the best teaching units in this country and was most influential in the origin and establishment of the McMillan Eye Institute. He served as Ophthalmologist-in-Chief, Barnes and Allied Hospitals, and was on the visiting staff of five other St. Louis General Hospitals, including the City and County Hospitals. He was loyal and conscientious in the fulfillment of his commitments.

In 1922 he became associate editor of the *American Journal of Ophthalmology* and in 1931 he succeeded William Crisp as Editor-in-Chief. This turned out to be a most arduous task, for there was at that time only an office girl to help. He spent many long and wearisome hours after a heavy day's work, going over manuscripts sometimes far into the night, until fatigue overwhelmed him. Things became easier when he discovered Miss Emma Buss, who was a superb manuscript editor and who proceeded to take much of the heavy burden out of his hands. In 1940 he developed anemia, which later was controlled, and felt that he must give up some of his multiform activities. Among these, and with considerable regret and soul searching, was the editorship of the *Journal*. However, when the new editor was called overseas to serve with the United States Army, Dr. Post resumed the editorship until 1945, when he, with considerable relief,

turned back his duties to his successor and was appointed a Consulting Editor, which position he held until his death.

Lawrence justly received many honors during his splendid career as a leader of American ophthalmology. He was elected President of the American Ophthalmological Society in 1951, the only president son of a president father in this oldest of special societies. He was President of the American Academy of Ophthalmology and Otolaryngology in 1944, and Chairman of the Section on Ophthalmology of the American Medical Association in 1941. He was a past Chairman of the Ophthalmic Section, Southern Medical Association, and a past President of the St. Louis Ophthalmological Society. He was a Fellow of the American College of Surgeons and a member of numerous other medical societies.

He was awarded the Howe Gold Medal of the American Ophthalmological Society in 1947 for his many outstanding contributions to American Ophthalmology, and in 1949 he received the Leslie Dana Medal for his work in the prevention of blindness.

He contributed much to ophthalmic literature by scientific papers and especially editorials in the *Journal* that reflected his great common sense and fairness. His influence for integrity, as exemplified in his many writings, was world-wide.

On March 28, 1953, on the occasion of his retirement as Head of the Department of Ophthalmology, his colleagues, expressing their deep admiration and affection for Larry, held a two-day scientific fiesta in his honor, and many papers were read by his friends and admirers from all parts of the United States. These papers were collected and published in a special number of the *American Journal of Ophthalmology* (36: [September] 1953) which was designated as the "Lawrence T. Post Issue." In this number is reproduced the handsome portrait of Lawrence donated to the school by his St. Louis associates and friends. At the banquet in his honor, more than one thousand friends, patients, and colleagues joined in many tributes to his sterling qualities as a man, friend, editor, scientist, teacher, and above all a physician.

Dean Robert A. Moore said on this occasion: "If all faculty members were like Lawrence, the life of a dean would be simple. Do not mistake me, he fights for what he thinks is right. But you know in advance that the discussion will be fair. Lawrence will listen to both sides of a question and his attitude will be generous even if he does not agree."

During all of these honest laudatory remarks and speeches, Lawrence squirmed and flushed with painful modesty and looked around as if seeking some way to escape. His final speech was forthright and most moving.

A few weeks later he suffered a cerebral vascular accident which left him partially paralyzed and affected his speech. Then began the five-year uphill struggle for rehabilitation, in which his devoted wife played a courageous and chief role. He succeeded to a remarkable degree in learning to talk again but was never able to resume much if any real activity, until death put an end to his tribulations.

The convivial side of Larry's character is one that all of his many close friends will ever cherish. When the occasion called for it, he was a gay and relaxed companion, joining his rather irregular voice in song with rare gusto. He loved life and once remarked with enthusiasm that he would not trade places with anyone in the world. We have indeed lost a rare person.

DERRICK VAIL, M.D.

## OLGA SITCHEVSKA, M.D.

### 1895-1958

The evening of May 20, 1958, marked the passing of a well-known ophthalmologist, Dr. Olga Sitchevska, of 30 5th Ave., New York.

Characteristic of her persistence, she had attended the clinic of the New York Eye and Ear Infirmary the preceding afternoon and interviewed a few patients on the day of her death. Precordial pain in the early evening caused her to seek aid in the emergency room of the New York Infirmary, where she had suffered her initial heart attack some weeks before. While recuperating from the preceding illness, she had almost completed a paper for publication.

Olga Sitchevska was born in Kiev, Russia, in 1895. She was graduated in medicine in the Medical School of Kiev University in 1918 and served an internship at Perm. In 1919 she entered the Russian military service for one year and came to the United States in 1923. She continued her training in ophthalmology and became an Assistant Surgeon of the New York Eye and Ear Infirmary in 1937. During that time, she was appointed Attending Ophthalmologist at the New York Infirmary. While progressing in her profession, she found time to publish thirteen splendid articles in professional journals and was the official translator of Russian articles for the *American Journal of Ophthalmology* and the *Archives of Ophthalmology*.

Dr. Sitchevska was a specialist certified by the American Board of Ophthalmology, a member of the New York County and State Medical Societies and the American Medical Association. She was a fellow of the New York Academy of Medicine and the American Academy of Ophthalmology and Otolaryngology. She was a member of the Association for Research in Ophthalmology and the Russian Medical Society.

The survivors are her husband, Constantine Shulakoff, and sisters and brothers in California.

Dr. Sitchevska was not only a talented ophthalmologist but she was a devoted friendly physician who enjoyed the complete confidence of her patients and friends. She spent many long hours with private and clinic patients alike. She enjoyed her work and was dedicated to the improvement of her specialty and to making the world a better place in which to live.

# News and Comment

## GENERAL NEWS

**Recommendations by the Motor Drivers Vision Committee of the Canadian Ophthalmological Society.**—These standards represent the best opinions of our time, but factual scientific data to back them is deficient, and therefore we must be prepared to change them as increasing knowledge may make it necessary.

1. Minimum vision standards

A. Standards

1. Heavy transport (over 6000 lb.)
   (*a*) Vision: 20/30 in one eye, 20/30 in other eye, with or without glasses
   (*b*) Fields: 120 degrees horizontal in each eye
2. Light transport (under 6000 lb.) and taxis
   (*a*) Vision: 20/30 in one eye, 20/60 in other eye, with or without glasses
   (*b*) Fields: 120 degrees horizontal in each eye
3. Private cars
   (*a*) Vision:
      (1) 20/40 in one eye, better than 20/200 in other eye, with or without glasses
      (2) 20/60 in one eye, better than 20/200 in other eye, with or without glasses; it is recommended the license should be endorsed "restricted to driving in daylight"
      (3) 20/40 in one eye, 20/200 in other eye or worse (including one-eyed), with or without glasses; it is recommended the license be endorsed "drive only with a rear view mirror located on the side with the poorer sight"
   (*b*) Fields:
      (1) 120 degrees horizontally in each eye
      (2) 120 degrees horizontally in better eye, but less than 120 degrees in other eye (including one-eyed); it is recommended that the license be endorsed "drive only with rear view mirror located on side with the poorer sight"

2. Restrictions

A. In order to make some of the standards acceptable, certain endorsements on licenses are advised, viz.

(*a*) If glasses are needed to pass the tests the license should be endorsed "drive only when wearing adequate eye glasses"

Private cars:

(*b*) Where the vision is only 20/60 in one eye but better than 20/200 in the other even with glasses, it is recommended that the license be endorsed "restricted to driving in daylight"

(*c*) Where the vision is 20/40 in one eye, 20/200 or worse in the other (including one-eyed), it is recommended that the license be endorsed "restricted to driving in daylight"

(*d*) Where the horizontal field is 120 degrees in one eye and less than 120 degrees in the other eye, it is recommended that the license be endorsed "drive only with a rear view mirror located on the side with the poorer sight"

**Eye Bank and Sight Conservation Society of Virginia.**—The Eye Bank and Sight Conservation Society of Virginia has been asked to be affiliated with the National Eye Bank, New York, and the Director, Dr. E. G. Gill, has been elected a member of the Council.

## ANNOUNCEMENTS

**Call for Papers.**—The 1959 meeting of the Section on Ophthalmology, American Medical Association, will be held in Atlantic City, N. J., June 8 to 12, 1959. Anyone wishing to present a paper before the Section is urged to communicate with Dr. Harold G. Scheie as soon as possible. A title and abstract of 50 to 150 words must be in his hands by Jan. 1, 1959. Anyone wishing to present a scientific exhibit should contact Dr. Frank W. Newell as soon as possible.

A $250 prize is offered for the best paper and another $250 prize, for the best scientific exhibit prepared for the Section on Ophthalmology at each Scientific Session.

Dr. Scheie, Secretary, Section on Ophthalmology may be addressed at 313 South 17th St., Philadelphia 3.

Dr. Newell, Representative to Scientific Exhibit, may be addressed at 950 E. 59th St., Chicago 37.

**New Orleans Academy of Ophthalmology.**—The Ninth Annual Meeting of the New Orleans Academy of Ophthalmology will be held in New Orleans in the Roosevelt Hotel, Feb. 23-27, 1959, featuring "Diseases and Surgery of the Retina."

The members of the panel are Drs. Arthur J. Bedell, Harold F. Falls, Bertha A. Klien, Dohrmann K. Pischel, Wilbur C. Rucker, Charles L. Schepens, Donald M. Shafer, and Lorenz E. Zimmerman.

The registration fee of $75.00 includes associate membership in the Academy for the year of 1959, as well as all other features of the convention. Hotel reservations should be made early by writing directly to the Executive Secretary, P. O. Box 469, New Orleans.

**Alumni Association of New York Eye and Ear Infirmary.**—The Annual Spring Meeting of the Alumni Association of the New York Eye and Ear Infirmary last April was so well received that it has been decided to expand next year's meeting, which will take place on April 20-23, 1959.

Symposia and lectures on pathology, traumatic surgery, and medicolegal ophthalmology will be conducted. It is also planned to offer refresher courses in gonioscopy and tonography, electrophysiology, radioisotopes, orthoptics, macular-function testing, and biomicroscopy.

More complete information regarding the meeting will appear in a later issue.

**Association for Research in Ophthalmology, Eastern Section.**—The meeting of the Eastern Section of the Association for Research in Ophthalmology will take place on Nov. 21 and 22, 1958, at Bellevue Hospital, in New York.

**Mary Putnam Jacobi Fellowship.**—The Women's Medical Association of the City of New York offers the Mary Putnam Jacobi Fellowship to a graduate woman physician, either American or foreign. This Fellowship will start Oct. 1, 1959, and will amount to $2000, $1000 being available Oct. 1, 1959. The recipient of the Fellowship will be expected to make a report to the committee at the end of the fourth month, following which the second $1000 will be awarded subject to the approval of the committee. The Fellowship is given for medical research, clinical investigation, or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the Fellowship, but exception may be made by the committee under special circumstances.

Applications for this Fellowship may be obtained from the secretary of the committee after Aug. 1, 1958, and must be returned before Feb. 1, 1959, with the following information: (1) curriculum viate, (2) a statement from a physician of a recent physical examination, (3) transcripts of college and medical school records, (4) personal letters of recommendation from two or more physicians under whom the applicant has studied, (5) a statement by the applicant of the problems she proposes to investigate or the study she plans to undertake, (6) a statement from the person under whom she proposes to study of his or her interest in the subject, and (7) a recent photograph. All the above data must be at hand before the application will be considered.

Successful candidates will be notified not later than May 1, 1959. The secretary of the committee is Ada Chree Reid, M.D., 118 Riverside Drive, New York 24.

**Special Lecture Series.**—Under the auspices of the Institute of Ophthalmology of the Americas, Prof. Dr. G. Meyer-Schwickerath of Bonn, Germany, will give a series of lectures on "The New Method of Light Coagulation in the Treatment of Fundal Pathology" on the following dates: Wednesday, Nov. 19, 1958, from 5-7 p. m.; Thursday, Nov. 20, 1958, from 5-7 p. m.; Friday,

Nov. 21, 1958, from 10-12 noon. Limited registration, fee $30. For further information, write Mrs. Tamar Weber, Registrar, 218 2d Ave., New York 3.

**Scheie to Give Schoenberg Lecture.**—The annual Schoenberg Memorial Lecture sponsored jointly by the New York Society for Clinical Ophthalmology and the National Society for the Prevention of Blindness will be given at 8:15 p. m. on Monday, Dec. 1, at the New York Academy of Medicine, 2 E. 103d St.

Harold G. Scheie, M.D., Professor of Ophthalmology at the University of Pennsylvania, will give an address on "Management of Infantile Glaucoma." This eye disease is an important cause of blindness among children because of its early effects on the retina and optic nerve, and Dr. Scheie has conducted research on its surgical treatment.

Mark J. Schoenberg, M.D., a New York ophthalmologist, was prominent in the work of both the National Society for the Prevention of Blindness and the New York Society for Clinical Ophthalmology. Since his death, in 1945, the two societies have joined each year in honoring his memory.

All physicians will be welcome.

**Association for Research in Ophthalmology, Inc., Future Meetings.**—Letters of intention to present papers may be immediately sent to the chairman of each meeting.

Western Section, Nov. 17-18, 1958, San Francisco, Stanford Eye Laboratory, 2018 Webster St. Frank C. Winter, M.D., 535 Middlefield Rd., Palo Alto, Calif.

Eastern Section, Nov. 21-22, 1958, New York, New York University, Bellevue Medical Center. Jerry H. Jacobson, M.D., 880 5th Ave., New York.

Southeastern Section, Dec. 6-7, 1958, Winston-Salem, N. C., Bowman Gray School of Medicine. Richard G. Weaver, M.D., Bowman Gray School of Medicine, Winston-Salem, N. C.

Midsouthern Section, No Meeting in 1958. Samuel B. Johnson, M.D., 611 Medical Arts Building, Jackson, Miss.

East Central Section, Jan. 5, 1959, Cincinnati, Netherland Plaza Hotel, Pavilion Caprice. Donald J. Lyle, M.D., 411 Oak St., Cincinnati.

Midwinter National Meeting, Feb. 19-21, 1959, Edgewater Park, Miss., Edgewater Gulf Hotel. James H. Allen, M.D., 1430 Tulane Ave., New Orleans.

Midwestern Section, April 18-19, 1959, Denver, Sabin Auditorium, University of Colorado. George S. Tyner, M.D., 324 Metropolitan Building, Denver.

National Meeting, June, 1959, Atlantic City, N. J. Lorand V. Johnson, M.D., 10515 Carnegie Ave., Cleveland 6.

With the object of reducing the number of sessions at the national meetings, the Board of Trustees have authorized the publication of a second supplement to contain papers presented at the section meetings. Authors wishing publication in this supplement should send their completed manuscript and any discussion to Lorand V. Johnson, M.D., as early as possible. The absolute deadline for this supplement will be Feb. 1. It is desired that this supplement, containing the membership roster and financial report for the fiscal year ending Dec. 31, may be published prior to the June national meeting.

Letters of intention to present at the June national meeting may be directed to the Secretary-Treasurer immediately. All abstracts for the June national meeting must be received by Dec. 15, 1958.

**Courses in Ophthalmic Surgery.**—New York University Postgraduate Medical School offers the following courses this fall:

Ophthalmic Plastic Surgery, a part-time course of five days' duration, 2 to 5 p. m., Nov. 17 through 21, 1958, under the direction of Dr. Sidney A. Fox. This course covers the essentials of ophthalmic plastic surgery for the practicing ophthalmologist. Instruction is by lecture and demonstration. Tui-

tion $85. This course is repeated 9 a. m. to 12 m. March 16 through 20, 1959.

Surgery of the Cornea, a full-time course of five days' duration, Dec. 1 through 5, 1958, under the direction of Dr. Ramon Castroviejo. This course is designed to cover current concepts and practices in the field of corneal surgery. Afternoons from 2 to 5 p. m. are devoted to didactic lectures, illustrated by lantern slides and motion pictures. During the mornings, as patient material is available, opportunity is offered to observe surgical procedures in the operating room. On the last morning of the course, students perform surgical procedures on animal eyes. Tuition $225.

**Postgraduate Course in Ophthalmology, State University of New York Upstate Medical Center at Syracuse.**—The Department of Ophthalmology of State University of New York Upstate Medical Center at Syracuse will present its Ninth Annual Postgraduate Course in Ophthalmology at the Hotel Syracuse on Friday and Saturday, Dec. 5 and 6, 1958.

The following lecturers will participate: Drs. John H. Dunnington, A. Edward Maumenee, and George K. Smelser.

The tuition fee is $25, payable to the State University of New York Upstate Medical Center at Syracuse, 766 Irving Ave., Syracuse 10. This fee covers tuition, daily luncheons, and dinner on Friday night. The course will be limited to 60 members. These will be accepted in the order in which applications, accompanied by checks, are received. Inquiries regarding the course may be addressed to Dr. James L. McGraw at the above address.

## SOCIETY NEWS

**Société française d'ophtalmologie.**—The French Society of Ophthalmology held its 65th yearly meeting in Paris, May 11 through 16, 1958. Many foreign members were present, mostly from Europe.

This year the main paper (*rapport*) was on "Embryology and Teratology of the Eye," written by Ch. Dejean, of Montpellier; François Hervouët, of Nantes, and G. Leplat, of Liège.

This is a very large book of 713 pages with 534 figures in black and white and 10 fine colored plates. This book is distributed free of charge to all members of the French Society. Nonmembers may obtain it by applying to the publisher, Masson & Cie, 120 boulevard Saint-Germain, Paris 6°. The price of the volume is 8000 francs (about $18.00). The first 500 pages deal with embryology, describing first that of the eye in general, then, in greater detail, the development of the different parts (retina, optic nerve, vitreous, lens, orbit, adnexae). The next 200 pages deal with teratology (anomalies of the retina, the optic nerve, the vitreous, the zonula, the lens, the iris, the ciliary body, the cornea, the lids, the muscles, and the lacrymal ducts and glands); there is also a chapter on anomalies of the whole eye (anophthalmia, microphthalmia, cyclopia). The book ends with an excellent bibliography of 44 pages and an index.

This main paper (*rapport*) was presented by the three authors on Tuesday, May 13, and this was followed by a discussion. In particular, O'Rahilly and Meyer (Detroit) reported an interesting study on embryology in the eye of the chick.

On Monday, May 12, the papers were devoted to the tumors of the conjunctiva. Mawas (Paris) stressed the necessity of examining carefully with the slit lamp the blood vessels of new growths of the conjunctiva, each variety of tumor having a special type of vascularization. He advised surgical removal and diathermocoagulation. Baclesse and Dollfus (Paris) spoke on the roentgen therapy of epitheliomas of the conjunctiva. Their paper was based on a study of 24 patients observed for at least five years. They considered that contact roentgen therapy was the best for tumors located near the limbus and penetrating roentgen therapy (180 kv.) was best for more extensive tumors. Vitte and Chardot (Nancy) observed a recurring nevo-carcinoma of the conjunctiva which had been originally removed two years before by diathermocoagulation; they resorted to a complete orbital exenteration; the result was satisfactory, but the patient was only observed

for one year. Offret and Lombard (Paris) reported a case of Libman-Sacks disease with conjunctival lesions which were similar to perforating scleromacia. They covered them with a buccal graft, with satisfactory results as long as the patient lived. Thomas, Cordier, and Algan (Nancy) stressed the difficulty of an etiological diagnosis in certain cases of conjunctivitis with affected lymph nodes (Parinaud's). Bietti and Ferraboschi (Rome) read a paper stating that statistical analysis convinced them that there was a link between keratoconus and vernal catarrh. Postic and Jelesic (Novi Sad, Yugoslavia) found herpetic virus in the anterior chamber of a patient with dendridic keratitis. Legrand and Baron (Nantes) believed that the tonsils are much more frequently the cause of ocular diseases than is usually accepted (uveitis, optic neuritis, Eale's disease, keratitis). Viallefont, Boudet, and Boulad (Montpellier) reported on satisfactory results in diabetic retinopathy with the new antidiabetic sulfonamides.

On Wednesday, May 14, the papers were on the choroid. Babel (Geneva) stressed the important part played by the choriocapillary in degenerative diseases of the macular area. François, Woillez, and Asseman (Lille) observed two patients who had had since childhood melanosis of the sclera and iris and who eventually developed a choroidal tumor leading to an enucleation. Ten Doesschate and Parren (Utrecht) reported that for several years they had treated melanosarcomas of the choroid by coagulating them with electrocoagulation (Weve's technique) and recently they had completed this treatment by photocoagulation of the central part of the tumor, which is not always easy to destroy by electrocoagulation. Ivan Stankovic (Belgrade) reported on a family tree of primary sclerosis of the choroidal blood vessels. This anomaly seemed linked to sex. Amalric and Bessou (Albi) read a paper on sclerosis of the choroidal blood vessel in vascular diseases. Bonnet (Lyons) stated that the diagnosis of generalized tuberculosis on the appearance of the fundus is not always certain, and he reported a case where, instead of tuberculosis, there was leptospirosis and another of similar appearance which proved to be sarcoidosis. Renard, Dhermy, and Mazel (Paris) operated on a patient for acute glaucoma, but pathological examination showed the presence of a malignant tumor in the uvea. Foucade and Couadau (Oran) read a paper on 30 cases of Reiter's disease. Remky (Munich) read a paper stating that streptococcus was often the cause of uveitis. Experimentally he observed two stages; first, an increase of toxins and a low amount of antibodies, and later a large amount of antibodies increasing beyond the amount of the toxins. Larmande and Giudici (Alger) reported on a case of Harada's disease.

Sunday, May 11, was devoted to free papers. Bessière and co-workers (Bordeaux) read a paper on ERG and adaptometry in glaucoma. Keiu Suda (Kumamoto, Japan) considered that important information could be obtained on glaucoma by bulbar compression: If after 10 minutes a 50 gm. pressure brings the tension down below 4 mm., there is no glaucoma, whereas if the tension remains above 8 mm. glaucoma is certain. Between 4 and 8 mm. glaucoma must be suspected. Ourgaud, Etienne, and Volla (Marseilles) thought that important information can be derived by a 10 mm. long tonography. Sedan and Aouchiche (Marseilles) believed that not enough attention has been paid to corneal anesthesia in glaucoma. Very often in this disease hypoesthesia goes with corneal neuralgia. Lavat and Canque (Paris) read a paper on orthoptics and surgical treatment in squint. Kluyskens (Ghent) stressed that in malingering the field studies are usually irrational, particularly when one compares centripetal and centrifugal tracings. Rougier and Wertheimer (Lyons) reported on a certain number of patients with what seemed to be typical choked discs and where careful studies obligated them to rule out an intracranial tumor. Zanen and Meunier (Brussels) read a paper on achromatic threshold in multiple sclerosis.

Thursday, May 15, was also given over to free papers. Appelmans and Michiels (Louvain) reported on a case of buphthalmia and hepatomegalia (Lowe's disease). Hervouet (Nantes) read a paper on an operation which he has been using satisfactorily after enucleation: He sutures the muscles to the sclera obtained from an eye bank, curettes the inside of the sclera carefully, and fills

it with an acrylic implant. Baron and Knejev (Nantes) stressed the use of acrylic shells to hold corneal grafts in place and also to protect corneal wounds. Maria, Bonnet, and Cochet (Paris) reported on their experience with the Strampelli lens. Rosselet and Stucchi (Lausanne) reported on late retinal vein thrombosis occurring after indirect cranial contusion. The link is not easy to explain, and the legal problem is often difficult to solve. Bouzas (Athens) stated that in leprosy cortisone injected under the conjunctiva was absorbed unusually slowly, small yellow nodes persisting sometimes for months and even years. Dugnani (Milan) demonstrated screens used in slit-lamp examination and photography of the anterior segment. Belz, Perdriel, and Guyard (Paris) gave a good description of corneal lesions due to freezing in pilots who had been exposed to very low temperatures. Arruga (Barcelona) reported on a technique with satisfactory results in detachment of the retina after diathermocoagulation. He passes a thread under the muscles, takes hold of the sclera between the muscles, draws the thread tight, and injects air into the vitreous after emptying the subretinal liquid. He finds this a satisfactory method for reducing the ocular cavity. Bregeat and co-workers (Paris) reported on a child of 11 years who had at the same time an orbital angiomatosis and an arteriovenous aneurysm in the mesencephalon. Thiebaut and Matavulj (Strasbourg) read a paper on ocular disturbances in multiple sclerosis.

The transactions of this meeting will be published toward the end of the year. Nonmembers will be able to obtain them from Masson & Cie, 120 boulevard St. Germain, Paris 6°. The price will probably be 8000 francs.

On Monday afternoon two symposia were held on ocular parasitosis, one on onchocercosis and other on toxoplasmosis.

On Tuesday afternoon several surgical films were presented.

On Monday and Thursday afternoons there were operations and demonstrations in several Paris hospitals.

On Tuesday evening the usual banquet was held, with Dr. Henri Moutinho, of Lisbon, presiding, and the next afternoon an excursion to Rheims was organized, with a visit to the cathedral and other churches and a pleasant ending in a champagne cellar (drinks were on the house!).

Several other ophthalmological organizations met during the same week: the International Organization Against Trachoma, the Society for Prevention of Blindness, and the Entretiens Therapeutiques.

The 66th meeting of the French Society of Ophthalmology will be held in Paris on May 10 through 14, 1959, and visitors are cordially invited even if they are not members of the Society and even if they do not speak French, since this year for the first time immediate translation in both English and Spanish was organized and proved most satisfactory.

# Books

**War Blinded Veterans in a Post War Setting.** Edited by Warren Bledsoe, Chief, Blind Rehabilitation, Physical Medicine, and Rehabilitation Service, Veterans' Administration. Price, $1.50. Pp. 260, index included. U. S. Government Printing Office, Washington 25, D. C., 1958.

This survey is one of a series of measures which the United States Government has undertaken as a means of helping those men who lost their sight in the last war. It records four major efforts directed to this purpose: (1) the action of the Army and Navy in activities centered around Avon Old Farms Convalescent Hospital, Valley Forge Army General Hospital, Dibble Army General Hospital, and the Philadelphia Naval Hospital; (2) the action taken by the Vocational Rehabilitation Education Service of the Veterans' Administration in the training of officers and vocational counselors under the direction of the American Foundation for the Blind; (3) the establishment of the Blind Rehabilitation Unit in the Veterans' Hospital at Hines, Ill., to serve the needs of veterans suffering postwar loss of sight from old eye injuries incurred in service and for those who might in any future military action lose their sight, and (4) the current survey. This survey has developed in four phases: (*a*) the personal interview between each blinded veteran and a Veterans' Administration Regional Office Social Worker; (*b*) the action carried out by the Regional Offices to assist blinded veterans when such action was recommended as a result of the interview; (*c*) a follow-up review of all those cases concerning which such action had been taken, and (d) the final phase, which has been concomitant with the second and third phases, consisting of an over-all review and tabulation of the data by machine analysis in the central office of the Veterans' Administration.

This book is obviously a compilation of much statistical data and cannot be reviewed as such. For those who are interested in this field, it contains a tremendous amount of factual material which will be of great value.

**Ophthalmic Plastic Surgery.** By Sydney A. Fox. Second edition. Price, $15. Pp. 324, including index, with 149 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1958.

The author of this well-known book on plastic surgery emphasized in his first edition that he was presenting a book based on his own experience and that it was to be judged from this aspect rather than as an attempt to include all the known facts and theories of plastic surgery applied to the eye. In this edition this principle has been strictly adhered to with very few exceptions. Recommendations are based on the author's convictions from his own cases, and, while many of these may be criticized by persons whose experiences do not coincide with those of Dr. Fox, the book consistently portrays the results of one man's experiences. This in itself creates a definite value and character not always found in other surgical texts. Only too often the author of such a book includes many worthless procedures, which he has not even tried, just because they appear in the literature. In this way much worthless material is perpetuated in print.

The illustrations are uniformly good, and the bibliography, while not completely brought up to date, since many newly recommended procedures have evidently not been tried by the author, is adequate for the text's purpose. This book can be recommended on the basis of the author's primary intent—to report on the results of his own experiences in ocular plastic surgery.

**Psychosomatic Ophthalmology.** By T. F. Schlaegel Jr., M.D. Price, $11. Pp. 523, with 21 tables. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

"The doctor who neglects the role of emotions robs himself and his patients of tools for diagnosis and therapy. . . . With the problems of infection almost

eliminated, disease processes are becoming mainly those of stress and degeneration. . . . We stand on the brink of a new epoch in which, by focusing the spotlight on the role of emotional factors, our knowledge of etiology is broadened. Such an increase in knowledge is the aim of the psychosomatic movement, and it is to that end that this book is dedicated." These excerpts from the author's preface give a fair statement of his purpose and his successful accomplishment in this book.

Part I concerns general psychosomatic and psychiatric conditions which influence the eye. The Freudian explanations of the "symbolic equivalence of eyes and genitals" with interesting examples in mythology seem a bit tenuous to the nonpsychiatrist reviewer, especially when direct etiological significance is implied between abnormalities of visual function and fear of castration. Part II considers an amazing number of general physical conditions with psychosomatic components which affect the eye, e. g., dermatologic conditions such as atopic eczema, collagen diseases, rosacea, and herpes simplex and zoster; neurological diseases including multiple sclerosis; headache, and other diverse conditions such as allergy, endocrine disturbances, musculoskeletal disturbances, cardiovascular and infectious diseases, and malignancy. Not only is the patient's emotional reaction to his illness stressed but heroic attempts are made to hypothesize etiologic relationships of the accompanying psychological disturbance to the organic manifestation of both the systemic and ocular disease.

Part III considers in detail a vast number of ocular diseases including many in which the psychosomatic component appears at the present time to be small. Much up-to-date nonpsychological ophthalmological information is included. The sections on refraction, functional field defects, and malingering with details of many tests for detection are particularly good. The "psychogenesis of uveitis" forms an interesting discussion, in which the author states that he believes that in about one-third of the patients the uveitis was precipitated by or prolonged by increased responsibility and stress. Arteriolar constriction, capillary dilatation and slowing of the blood stream, and anoxia with increased permeability and exudation can result from neurovascular reactions both from manifestations of stress and fatigue and locally from noxious organisms. Rest and psychologic regression (relief from stress and responsibility, especially when in the hospital) are considered of value in treatment.

Part IV details the psychosomatic approach to treatment, and this seems to be the most useful part of the book as far as suggestions for the management of these types of patients are concerned. The psychological aspects of surgery both for children and adults, the problems of the blind, and recent pharmacotherapy are all superbly discussed.

Dr. Schlaegel has covered a vast amount of literature, including many interesting tidbits of folklore. However, most of this is presented uncritically, providing, at times, only weak reeds of evidence for cause-and-effect relationship of psychosomatic factors and etiology of certain types of ocular disease. If a patient with an ocular disorder also has a psychological peculiarity, the two are often implied to be related. It goes without saying that this type of apparent relationship requires the strictest type of controls because of the psychological peculiarities of most of us without ocular disease. In many of the case reports the direct relationship is vague, and in certain cases little information of the result of psychotherapy is given. At times, the psychosomatic explanation of an ocular disease becomes exceedingly involved in attempting to lay it at the feet of Oedipus (a Greek legendary figure who tore out his eyes because he had killed his father and married his mother). Other explanations involving the neurovascular, autonomic, and hormonal systems seem more in line with current physiological concepts.

This very readable book is valuable in stressing an aspect which is often overlooked by busy ophthalmologists, and it is certainly provocative in suggesting psychosomatic factors in ocular diseases which were thought to be entirely organic.

**Concepts of Classical Optics.** By John Strong. Price, $9.50. Pp. 713, with 414 illustrations. W. H. Freeman and Co., 660 Market St., San Francisco 4, 1958.

While this book goes far beyond the knowledge of optics required for the ophthalmologist, it is becoming increasingly evident that the average level of optical wisdom, let us say, among ophthalmologists is lamentably low. In all fields of science which is applied practically, it is recognized that the basic information needed by those who make the practical application of the science can be set at a relatively low level. The selected few who are expected to advance knowledge in that field must necessarily have more than a speaking acquaintance with the basic facts, and if the whole group is a healthy one it will be evident that a certain small number from the group are consistently advancing the current horizon in their writings. It is a sad commentary, but this is not true in ophthalmology. Since the days of Gullstrand there have been very few ophthalmologistst who have added to our theoretical knowledge. Most of the advances in optics have been made by pure physicists. It is time to take stock and find out why ophthalmologists are not represented in this selected group. Obviously the chief reason is that those few persons, call them geniuses if you will, become so interested in the primary science that they leave the field of applied optics and hence never become ophthalmologists. This reviewer knows of several examples of men who started out to be ophthalmologists but who have since left the fold and have become full-time physicists in the field of optics. This book will undoubtedly appeal to just these men, and, by the same token, most ophthalmologists will shun it because it is beyond their interest or, what is more likely and more to be ashamed of, because it is beyond their understanding.

The book consists of a series of chapters on classical optics by the author, requiring a knowledge of calculus, vectors, and complex numbers for its understanding. An appendix follows, written by various authorities in the fields represented. Unless our education in optics materially improves, this book will not even be understood by our advanced students.

**The Cerebrospinal Fluid: Production, Circulation and Absorption.** A Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme and Cecelia M. O'Connor. Price, $9. Pp. 335, index included, with 141 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This is another Ciba Foundation Symposium by experts in the field of cerebrospinal fluid. The following chapters illustrate the ground covered:

Structural and Functional Changes in the Telencephalic Choroid Plexus During Human Ontogenesis, by J. Ariens Kappers.

The Structure and Relationships of the Arachnoid Granulations, by Leslie Turner.

The Fine Structure of the Mammalian Choroid Plexus, by George B. Wislocki and A. J. Ladman.

Nerves of the Meninges and Choroid Plexus, by E. R. A. Cooper.

Observations on the Choroid Plexus Maintained as an Organ in Tissue Culture, by C. E. Lumsden.

Observations on the Production and Circulation of the Cerebrospinal Fluid, by D. H. M. Woollam and J. W. Millen.

Studies of the Formation and Absorption of the Cerebrospinal Fluid Using Radioactive Isotopes, by B. Selverstone.

Vitamins and the Cerebrospinal Fluid, by J. W. Millen and D. H. M. Woollam.

Some Aspects of the Relationship Between the Cerebrospinal Fluid and the Central Nervous System, by H. Davson.

The Existence of a Barrier Between the Cerebrospinal Fluid and the Boundary of the Brain, Including Experimental Investigations on Rabbits, Using Bilirubinemia, by L. Herlin.

Neuropathological Observations on the Cerebrospinal Fluid Pathway, by K. J. Zulch.

Mechanical Aspects of the Cerebrospinal Fluid Circulation: Physiological, Pathological, Surgical, by Norman M. Dott and F. John Gillingham.

Clinicopathological Aspects of the Cerebrospinal Fluid Circulation, by R. T. Johnson.
A Possible Mechanism of Hydrocephalus: The Osmotic Regulation of Cerebrospinal Fluid Volume, by D. Bowsher.
Some Problems of Experimental Spinal Anaesthesia, by A. D. Macdonald.

The valuable part of all these symposia is, of course, the discussions, which have been reprinted in full in each volume. This book will be of great value to all those interested in the physiology of the cerebrospinal fluid and necessarily that of the aqueous humor, since these two fluids have so much in common in their origin and fluid dynamics.

**The UFAW Handbook on the Care and Management of Laboratory Animals.** Edited by A. N. Worden and W. Lane-Petter. Second edition. Price, $9.80. Pp. 951, profusely illustrated. Universities Federation for Animal Welfare, 7-A Lambs Conduit Passage, London W. C. 1 (distributed in U. S. by Animal Care Panel, Office of Editor, 951 E. 58th St., Chicago 37), 1957.

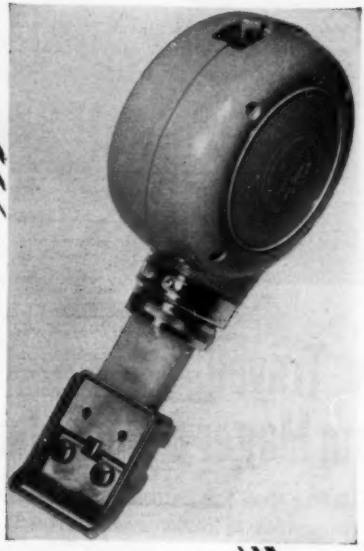
The first edition of this handbook was published ten years ago. Since then, knowledge has developed rapidly in the care and handling of laboratory animals, with the result that this second edition is considerably enlarged over the first. It will be useful for all workers in the experimental sciences where animals are used. There are chapters on the legal protection of laboratory animals, the animal house and its equipment, pests and their eradication, breeding methods, nutrition and handling of laboratory animals, anesthesia and euthanasia, and the laboratory animal business in the United States. This section is followed by chapters on each individual experimental animal, including the entire animal kingdom from earthworms to the horse.

The book is beautifully printed and illustrated and contains an excellent bibliography at the end of each chapter and a good index.

storz
Surgical Instruments

# Electro-Keratotome *for the* Dissection *of* Lamellar Grafts

**RAMON CASTROVIEJO, M.D.**



Procedure is shortened, and minimally traumatized grafts of even thickness and as large as permitted by the donor's eye are obtained. This result was difficult to achieve by older methods, especially with larger grafts.

- Small enough to observe the donor eye for which it is used only.
- Edge of cutting blade visible through open roller guards, enabling surgeon to start and complete graft at exact margins.
- Uses small, disposable, double-edged razor blade. Simple mechanism.
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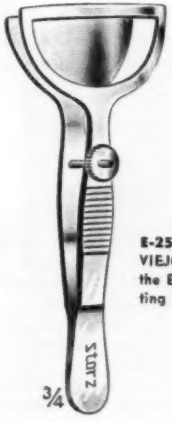


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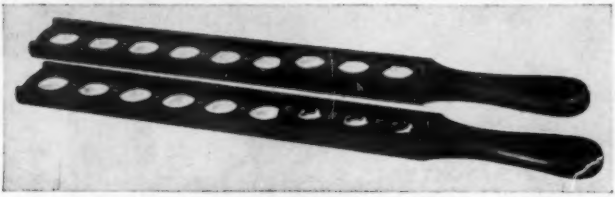

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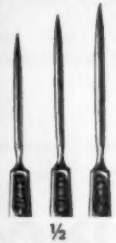

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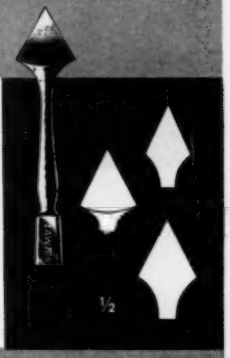

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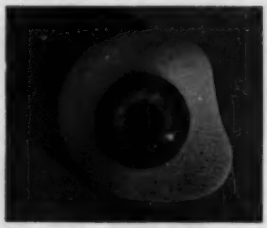

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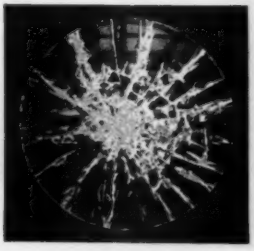

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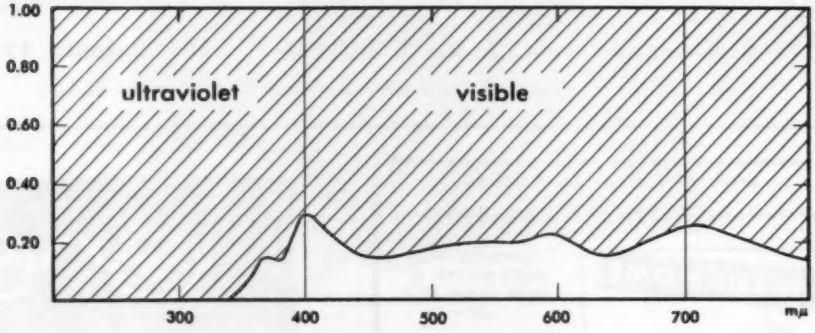


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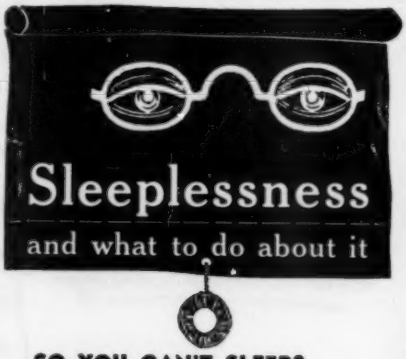


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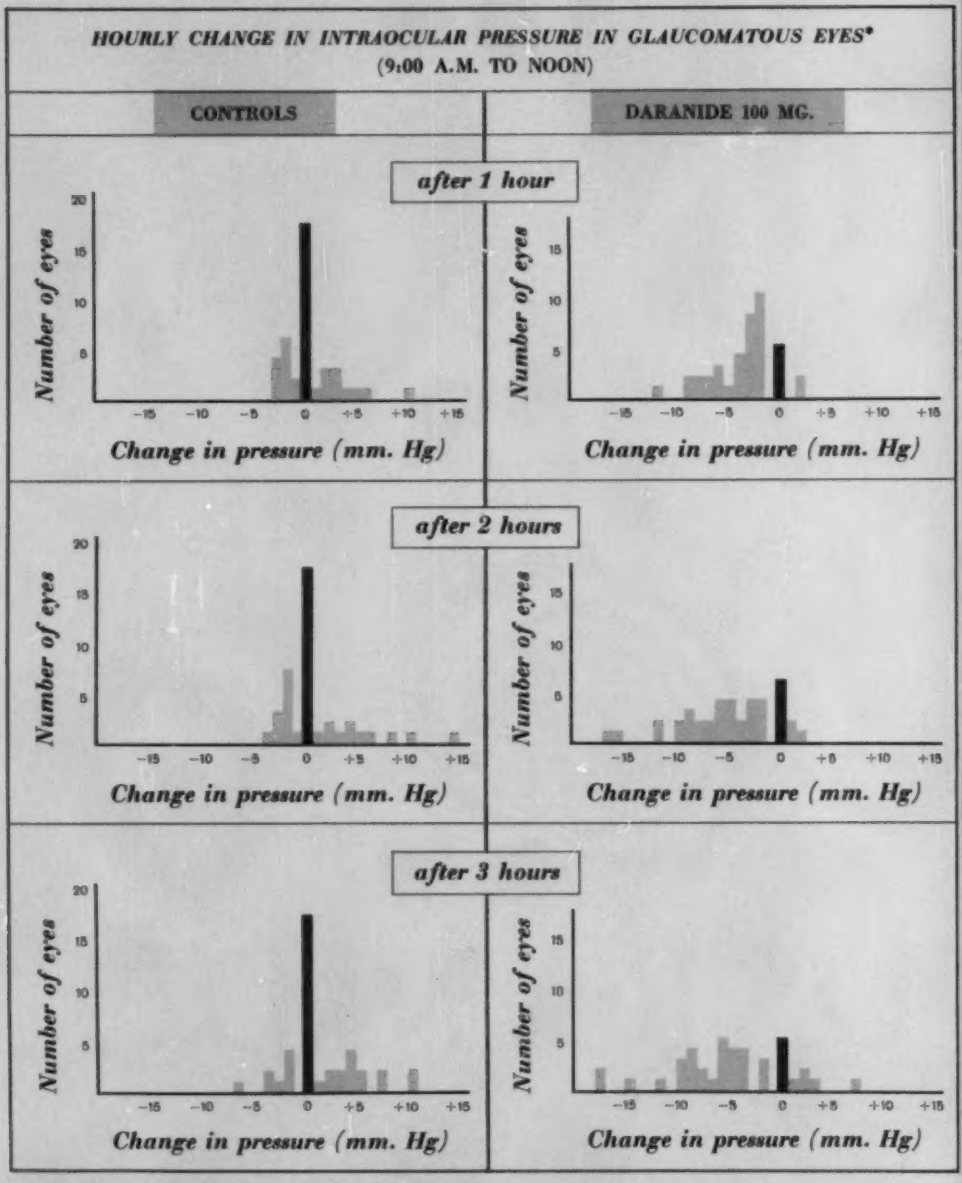
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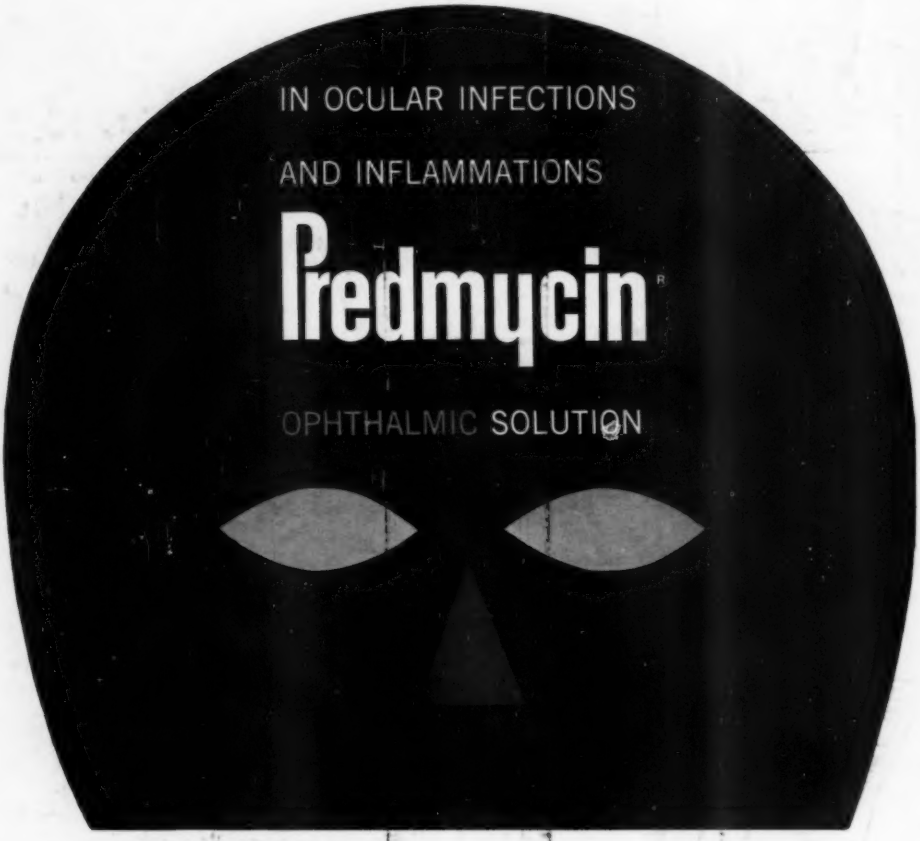


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- *for the patient: Phenylephrine HCl for rapid improvement of the eye's appearance*
- *for the pathogen:* Neomycin sulfate for its wide antibacterial effectiveness against most pathogens responsible for ocular infections
- *for the inflammatory process:* Prednisolone for its rapid and effective action in checking destructive inflammatory reactions to ocular trauma.

Predmycin combines prednisolone alcohol 0.2%, neomycin sulfate 0.5%, and phenylephrine HCl 0.12%, in a sterile, lubricating solution—for optimal control of infectious, inflammatory and allergic conditions of the eyelids, conjunctiva, cornea, sclera, uveal tract, and following thermal or chemical burns.

**DOSAGE:** 1 to 2 drops in the eyes two to four times a day.

**SUPPLY:** In 5 cc. all-plastic dropper bottles—on prescription only.

ALLERGAN CORPORATION *Los Angeles 17, California*